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The American Heart Journal

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Original Communications

ACUTE ISOLATED MYOCARDITIS*

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THIS paper deals with the clinical and pathological observations on two cases of acute myocarditis, which is described in past writings as acute isolated diffuse myocarditis, acute isolated interstitial myocarditis, and Fiedler's myocarditis. These terms are used to designate a rare form of heart disease which presents both clinically and pathologically a picture different from that seen in other inflammatory lesions of the myocardium. The clinical picture in all recorded cases is clearly one of progressive myocardial failure, rapid in some cases, more gradual in others, but unassociated with any of the better known factors leading to heart failure. That such cases as have been reported were obscure, so far as etiology is concerned, is indicated by the fact that in no instance of the recorded cases which came to autopsy was a correct antemortem diagnosis made.

In the majority of instances the heart shows varying grades of hypertrophy and dilatation post-mortem. The myocardium alone is diseased, while the pericardium, endocardium and heart valves are not affected. Histologically, the inflammatory changes are confined largely to the interstitial tissues, although some authors find the parenchymatous tissue also involved. There is a diffuse infiltration of lymphocytes and polymorphonuclear leucocytes, especially eosinophiles, in the interstitial spaces. Aschoff[1] reports a case showing eosinophiles, plasma cells, lymphocytes, and a few fibroblasts, with slight necrosis of the muscle fibers. He mentions specifically that no rheumatic nodules were found.

The first clear account of this disease was given by Fiedler[2] in 1890, although two years earlier Steffen[3] reported two cases of acute myocarditis which probably fall in this classification. In a review of publications on the subject, we found reports of 36 cases with post-mortem study. The pertinent data of 30 cases in this group are contained in Table I.

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TABLE I

SUMMARY OF PREVIOUSLY RECORDED CASES OF ACUTE ISOLATED MYOCARDITIS CONFIRMED BY AUTOPSY*

NO.	AUTHOR	YEAR	AGE OF PATIENT	SEX	HEART	POSSIBLE ETIOLOGY	REMARKS
1	Steffen	1888	Between 45-50	–	Dilated		
2	Steffen	1888	50	–			
3	Freund	1893	40	♀	Dilated		
4	Rindfleisch	1898	34	♂	Hypertrophic		Blood culture showed staph. citreus.
5	Josserand		25	♂	Hypertrophic		
6	and	1901	29	♂	Hypertrophic		
7	Gallavardin		27	♂	Hypertrophic		
8	Zuppinger	1901	3	♂	Hypertrophic and dilated	Phlegmon left foot	
9	Zuppinger	1901	41	♂	Dilated	Burn	
10	Aschoff	1904	--	–			
11	Selletin	1904	16	♂	Hypertrophic	Carbuncle	
12	Selletin	1904	24	♀			
13	Förster	1905	6	–	Hypertrophic		
14	Saltykow	1905	37	♂	Hypertrophic	Abscess of neck	
15	Saltykow	1905	--	–	Enlarged		
16	Baumgartner	1916	20	♀	Hypertrophic		Possibly tbc. myocarditis.
17	Pal	1916	16	♀	Normal size	Gonorrheal urethritis	
18	Gierke	1921	25	♀	Hypertrophic		Possibly syphilitic myocarditis
19	Fiebach	1921	33	♀	Hypertrophic	Upper respiratory infection	
20	Fiebach	1921	63	♂	Enlarged		
21	Schilling	1921	22	♂	Hypertrophic		
22	Schilling	1921	63	♀	Hypertrophic		
23	Schmincke	1921	26	♀		Influenza	Early acute verr. endocard.
24	Hafner	1922	26	♀	Hypertrophic and dilated	Influenza	
25	Stolz	1922	21	♂	Hypertrophic	Rheumatism	
26	Lemke	1924	52	♂			
27	Lemke	1924	71	♀	Normal size	Pneumonia	Called acute parenchymatous myocarditis
28	Mordre	1924	41	♂			
29	Kaufmann	----	--	–		Infected burn	
30	Kaufmann	----	--	–		Infection of operative field	

*Fiedler's[2] origial four cases and one case each reported by Cohn[10] and Wolf[24] are not included in the above table because the original papers were not available to us.

The etiology of the disease is not determined. Aschoff[1] suggests that it probably has an infectious or toxic origin. Kaufmann[4] holds that it is due to the toxic action of bacterial products rather than to bacteria, since the latter have never been found in the myocardial lesions. Kauf-

mann refers to two cases that he has seen; one followed an infected burn which, however, healed, and the other followed an infection of the operative field due to the removal of tuberculous lymph nodes of the neck. Some writers associate the myocardial changes with certain infections which either antedated or which were present at the time of death. For example, Pal's[5] case was treated for acute gonorrheal urethritis two months prior to the onset of heart failure. Hafner's[6] patient developed myocardial insufficiency two months after an attack of influenza and died one month subsequently. In still other instances, there was no evidence of infection associated with the myocardial lesion,

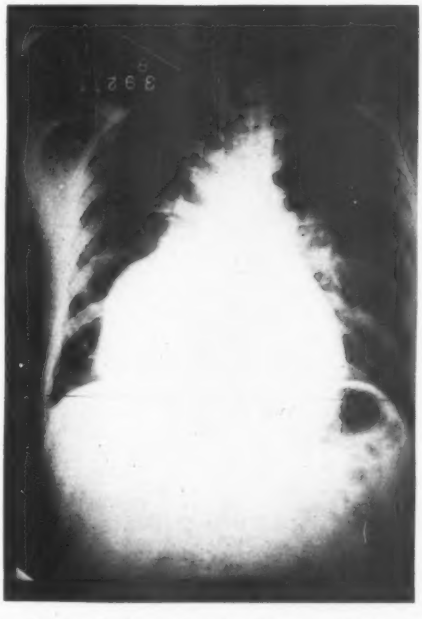

Fig. 1.—X-ray (7-foot plate) of the heart in Case 1. Note the marked increase in the cardiac shadow to the right of the midline.

so that the attempts of past writers to establish the etiology of this form of acute myocarditis must be regarded as unconvincing.

Following are the observations we have made on two cases which appear to be examples of Fiedler's myocarditis.

CLINICAL REPORTS

CASE 1.—The patient, W. B., a white male, 36 years old, was admitted July 28, 1927, and died October 22, 1927. His chief complaint was shortness of breath and pain over the liver.

Past History.—He had the usual diseases of childhood and gave a vague history of a migratory arthritis at the age of 16, which, however, did not confine him to bed and for which he had no treatment. At the age of 26 he had an illness which forced him to stop work for nine months. This developed gradually, with dyspnea on exertion, and a few weeks later edema of the ankles appeared. After

nine months he recovered and returned to his work as a clerk in the courts. From this illness to the present one, ten years had elapsed, and during that time he had no illness and had been able to indulge in such activities as baseball and hockey with no undue breathlessness.

Present Illness.—Eighteen months before coming under our observation, the patient had an attack of influenza which confined him to bed only two days but which he regarded as marking the onset of his present difficulty. For the past year, he had more or less respiratory distress on exertion and lost considerable time from his work because of this symptom. He occasionally noticed slight edema of the ankles and tenderness over the liver. With rest in bed and digitalis for a few days, he recovered sufficiently to return to his work, only to fail again in a few weeks. The patient had been an invalid for two months before admission to the hospital.

Physical Examination.—This revealed a well-developed and well-nourished white male in no acute distress but with a rather marked systolic pulsation of the carotid arteries. There was no venous distension in the neck.

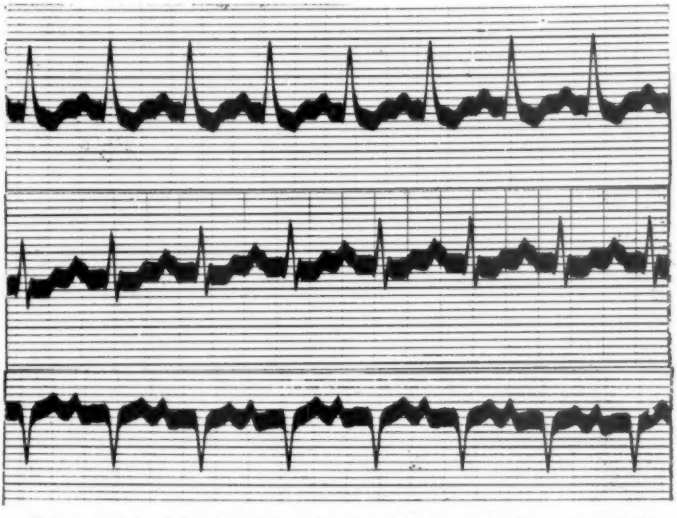

Fig. 2.—Three standard leads of the electrocardiogram in Case 1. In this and subsequent curves vertical lines represent time in 0.2 and 0.04 of a second; horizontal lines equal 10^{-4} volts.

Heart: There was a marked and extensive precordial activity visible over the upper part of the chest, most marked in the region of the right nipple. Palpation disclosed an unusual duplication of each cardiac impulse of about equal force. No definite apical impulse was distinguished. On percussion the limits of cardiac dullness extended to the left of the midline 9 cm. in the fourth and fifth intercostal spaces, and to the right of the midline 8 cm. in the third and fourth intercostal spaces. A seven-foot x-ray plate of the heart taken two days after admission is shown in Fig. 1. The cardiac shadow is greatly increased, particularly to the right of the midline. Auscultation over the apex revealed soft and muffled heart sounds, but no murmurs were heard. Approaching the base of the heart, the first sound was almost inaudible, but the second sound was loud, harsh and rasping. In the second intercostal space to the right, the sounds were again distant and almost inaudible. The heart sounds were loudest in the fourth right intercostal space, just inside the right nipple. Here one heard three heart tones equally spaced, the first two sounds corresponding to the double impulse described above.

A few moist râles were heard at the left lung base, otherwise the lungs showed nothing unusual. The liver edge was palpated 3 cm. below the costal margin; it was tender and pulsating. The pulses in all the accessible arteries were regular but very soft and easily compressible. The rate was 85 per minute and the systolic blood pressure was 100 mm. Hg. There was no thickening of the arterial walls demonstrable. The blood picture was normal, the blood Wassermann was negative, and the urine showed nothing unusual.

Clinical Course.—During the three months that this patient was under observation, he had a low grade fever with daily elevations to 38.2° C. Blood cultures were negative. The heart rate varied from 90 to 110 and the systolic blood pressure between 90 and 100 mm. Hg. No satisfactory determination of the diastolic blood pressure could be made. The cardiac findings showed little change. Two electrocardiograms were made; one on August 1, 1927 (Fig. 2), and the other October 19, 1927 (Fig. 3). These show moderate left ventricular preponderance. The changes in the S-T segment in Leads I and II are probably

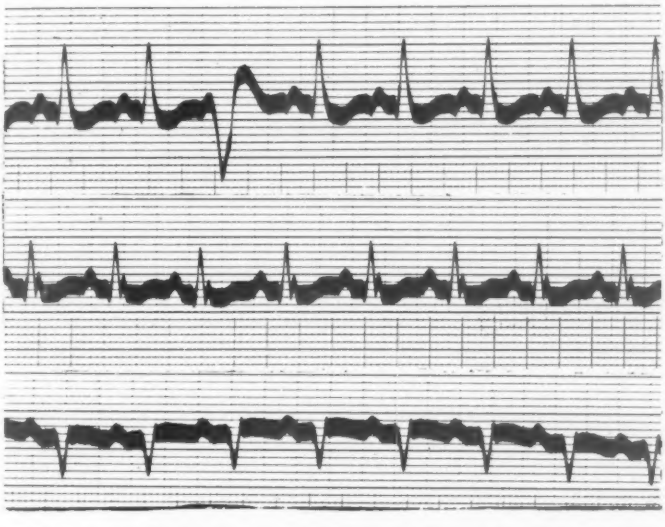

Fig. 3.—From the same patient, 79 days after Fig. 2.

due to digitalis. The patient gradually failed, the signs of congestion became more marked, and he died October 22, 1927.

The following clinical diagnosis was submitted: Rheumatic myocarditis; cardiac hypertrophy and marked dilatation; adherent pericardium (?); death due to myocardial insufficiency.

Pathological Report.—The autopsy was performed four hours after death. The body was that of a well-developed and well-nourished, adult white male, 36 years old. There was marked edema of both lower extremities and the subcutaneous tissues were very moist. The left pleural cavity contained 600 c.c. of a straw colored, clear liquid, but the pleural surfaces were smooth and glistening, and there were no adhesions. The other body cavities appeared normal. Multiple red infarcts were found in the lower lobe of the left lung, and old and recent infarcts were present in both kidneys. Both the liver and kidneys showed extensive cloudy swelling. Except for marked chronic passive hyperemia the other abdominal viscera showed no gross pathological changes.

Heart: The heart weighed 600 grams. The organ was globular in shape and

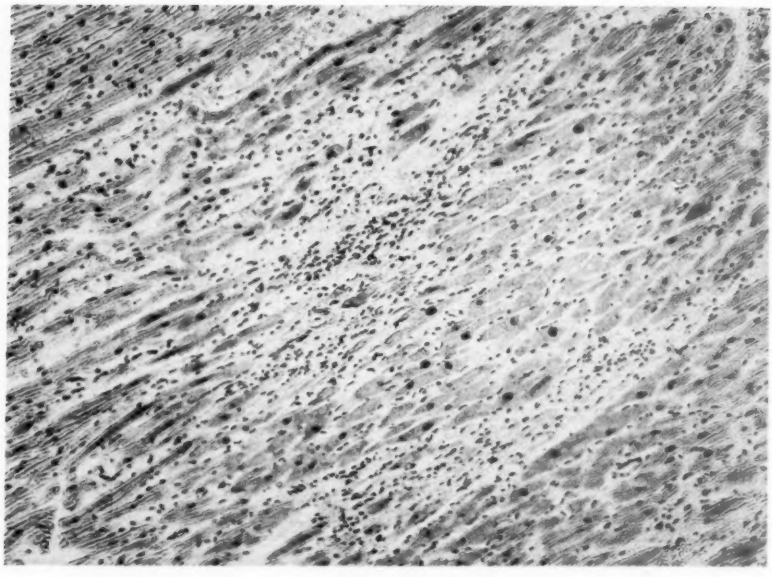

Fig. 4.—Section of myocardium, Case 1. Hemosiderin-eosin stain x 60. Description in text.

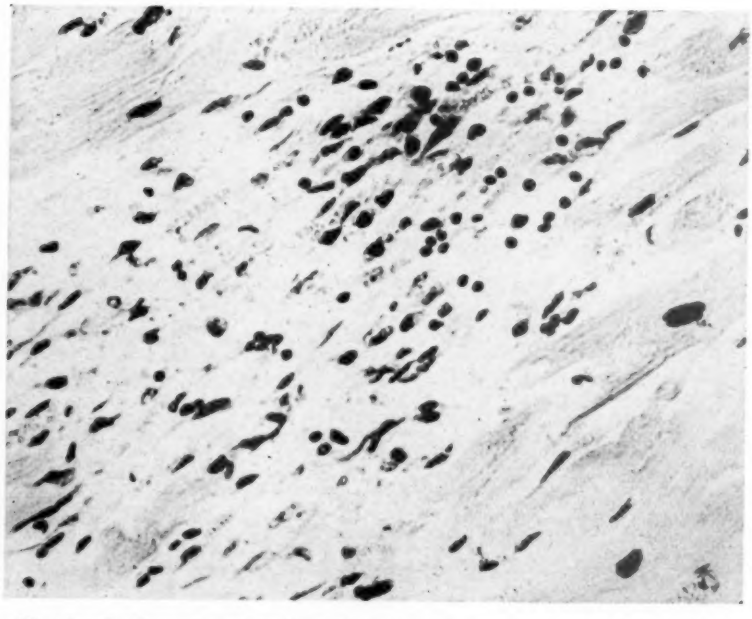

Fig. 5.—Section of myocardium, Case 1. Hemosiderin-eosin stain x 300.

markedly enlarged in all chambers. The apex was very flabby, rounded, and formed in part by the right and in part by the left ventricle. The epicardium was smooth and glistening throughout, and the coronary vessels were not diseased. The mural endocardium of the right ventricle showed several thrombi, grayish-red in color, which were firmly attached to the wall. The valves throughout were tender and delicate and showed no retraction or fibrosis. The aortic valve showed only two leaflets. The mitral valve had a circumference of 16 cm., the aortic 8 cm., the pulmonary 10.5 cm., and the tricuspid 16 cm. The sinuses of Valsalva were smooth. The papillary muscles and columnae carneae were hypertrophic and flattened. On cut section the myocardium was reddish-gray in color; it showed a coarser architecture than normal and contained many grayish-yellow streaks.

Microscopical Description.—The heart muscle fibers were larger than normal, the striations were obscure, and the nuclei showed squared ends and appeared swollen. Throughout the interstitial tissue there was an extensive infiltration of endothelial cells, plasma cells, and lymphocytes (see Figs. 4 and 5). The endothelial cells in some fields had a dark, slightly granular cytoplasm with sharply defined nuclei, but no Aschoff bodies or necrotic areas were seen. A few areas showed in addition polymorphonuclear leucocytes and many eosinophiles. Fibroblasts were seen in some fields; in others, small blood vessels around which were many lymphocytes, endothelial cells and polymorphonuclear leucocytes. Only a few sections showed these inflammatory cells invading the heart muscle fibers. There was a slight increase in connective tissue, but no fibrin or giant cells were noted. In a few sections were seen segmentation of the heart muscle fibers. Sections stained with Gram-Weigert stain showed no bacteria. Similarly the Warthin-Starry and Levaditi method gave a negative result for spirocheta pallida.

Pathological Diagnosis.—Acute myocarditis; hypertrophy and dilatation of the heart; relative insufficiency of mitral, tricuspid and pulmonary valves; mural thrombi of the right ventricle; multiple infarcts of left lung and both kidneys.

CASE 2.—The patient, S. W., a colored male laborer, 48 years old, was admitted to the Psychopathic Division of the Cleveland City Hospital, September 16, 1927, because of mental symptoms, but it was apparent on examination that he was suffering from heart disease. Exact information concerning the duration and progress of the present illness was not obtained. However, it was learned that the patient worked as a laborer until seven months before admission when he stopped because of breathlessness on exertion. During this period he was not incapacitated, he had no objective signs of circulatory failure and continued to go about until a few days before coming under our observation.

Past History.—There was a vague history of a penile lesion fifteen years ago. The patient had always worked as a day laborer and had never been confined to bed. He was the father of ten living children, and the wife's history showed no miscarriages. He was a moderate drinker but consumed no narcotic drugs.

Physical Examination.—The physical examination revealed the typical clinical picture of a patient suffering from moderate circulatory failure. In the semi-upright position the veins of the neck were engorged, and he was obviously dyspneic. The lungs were clear except for râles of congestion at both lung bases. There was no visible apical thrust, but palpation revealed a rather diffuse, feeble apex beat in the sixth intercostal space, 2 cm. to the left of the midclavicular line. The first heart sound was entirely replaced by a systolic murmur, and over the conus and base of the heart the sounds were muffled but no murmurs were heard. The cardiac mechanism was normal but was interrupted occasionally by an extrasystole. The pulse in the accessible arteries was markedly diminished in volume, and the blood pressure was 130/100 mm. There was moderate sclerosis of the arterial walls. The liver was 2 cm. below the costal margin and tender. Other-

wise examination of the abdomen was negative. There was moderate edema over the sacrum and over the shins. The patient had no fever, a normal blood picture, and except for albumin the urine showed nothing unusual. Tests for syphilis in both blood and spinal fluid were entirely negative.

Fluoroscopically the heart showed a marked increase in the transverse diameter, particularly to the right. This is shown in the seven-foot x-ray plate reproduced in Fig. 6.

Clinical Course.—The patient showed no signs of improvement during the forty-eight days that he was under observation. A week before death his temperature rose abruptly to 39.5° C., and then continued as a septic type of fever until he expired. The congestive failure increased, the heart sounds became feebler, the blood pressure gradually dropped to as low as 85 mm. systolic, and in this con-

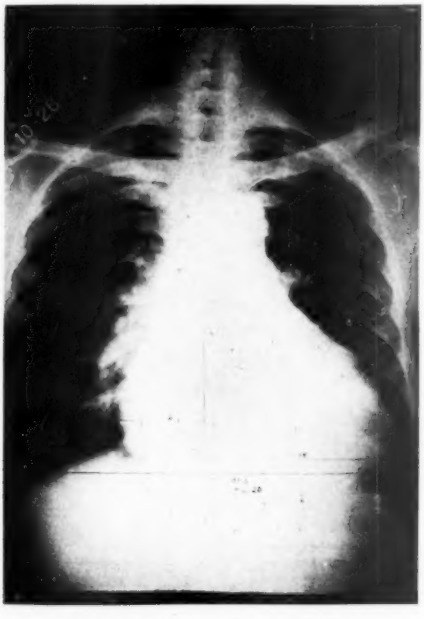

Fig. 6.—X-ray photograph (7-foot plate) of the heart in Case 2. Note the increase in the cardiac shadow both to the right and left.

dition he died. Five days before death an electrocardiogram (Fig. 7) was taken which shows left ventricle preponderance but otherwise nothing remarkable.

From the clinical observations on this patient it was apparent that death resulted from circulatory failure, but in the absence of hypertension, and with no clear evidence of valve disease, the etiology of the heart failure was obscure. After much discussion, the following clinical diagnosis was submitted: Coronary arteriosclerosis; myocardial fibrosis; cardiac hypertrophy and marked dilatation; death due to circulatory failure.

Pathological Report.—The body was that of a well-developed and well-nourished adult colored male with marked edema of both lower extremities. Both pleural cavities contained a small amount of fluid, but the pericardial and peritoneal cavities appeared normal. Infarcts were found in the left lung, in both kidneys and in the spleen. Both the liver and the kidneys showed marked cloudy swelling. Chronic passive hyperemia was found in all the viscera.

Heart: The organ was soft and friable, dilated in all chambers and weighed

700 grams. The coronary vessels were not tortuous and showed only minimal intimal changes with no calcification or thrombosis. Several firmly attached thrombi were found in the endocardium of the left ventricle, where a few circumscribed areas of endocardial fibrosis were seen. The heart valves were carefully inspected, but no old or recent changes were found. The aortic valve was 8.5 cm. in circumference, the mitral 13 cm., the pulmonary 9 cm., and the tricuspid 14 cm. The papillary muscles were large and flattened. The architecture of the myocardium on cut section was obscured, and throughout there were many small, soft, red and yellow areas, but no infarction was found. The right ventricular wall measured 3 mm. in thickness and the left 15 mm.

Microscopical Description.—There is a marked infiltration of lymphocytes, endothelial cells and polymorphonuclear leucocytes in the interstitial spaces (see Figs. 8 and 9). However, a few sections show these changes also in the parenchymatous

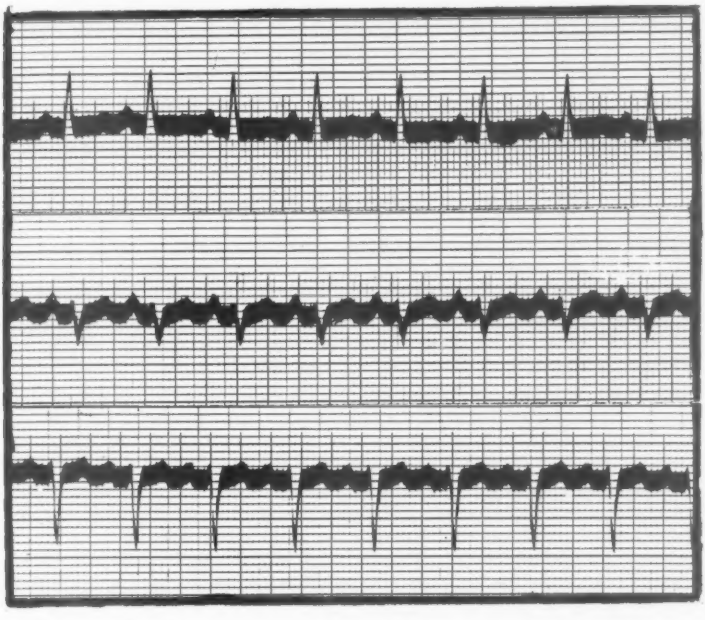

Fig. 7.—Three standard leads of the electrocardiogram in Case 2 showing a normal mechanism with moderate preponderance of the left side.

tissue. In some sections, endothelial cells and lymphocytes predominate, while in others one sees many eosinophiles and a few plasma cells. Large endothelial cells with eccentrically situated nuclei, together with a few myelocytes and polymorphonuclear leucocytes are found. Some fields show massive infiltrations of these cells. In some sections there is a new formation of small blood vessels which show extravasations of red blood cells, together with lymphocytes and endothelial cells. No increase in connective tissue is observed. The heart muscle fibers appear swollen, the cytoplasm granular, and there is a definite loss of striation. In some fields showing marked inflammatory changes, the muscle fibers are shattered. No giant cells or Aschoff nodules are seen. A careful search for bacteria and for spirocheta pallida gave a negative result.

Pathological Diagnosis.—Acute and subacute myocarditis; hypertrophy and dilatation of heart; mural thrombi of the left ventricle; multiple infarction of lungs, spleen and kidneys.

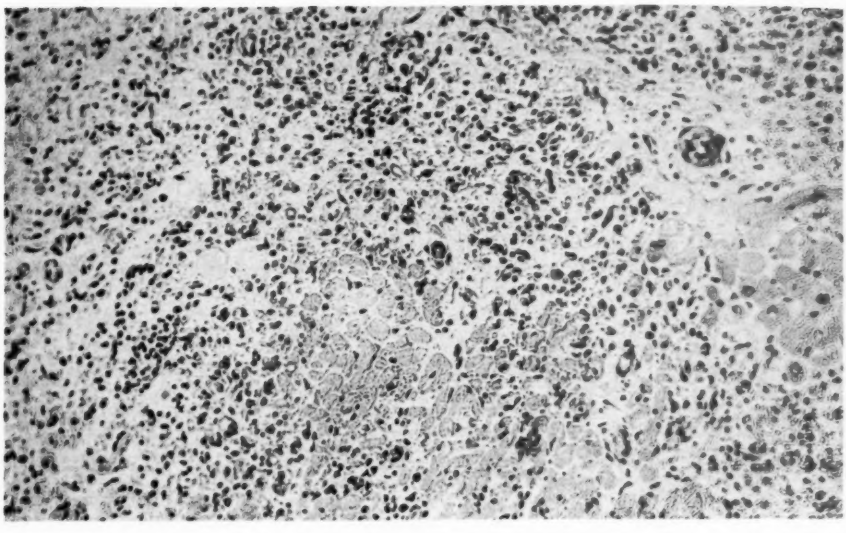

Fig. 8.—Cross-section of the myocardium in Case 2. Hemosiderin-eosin stain x 120. Description in text.

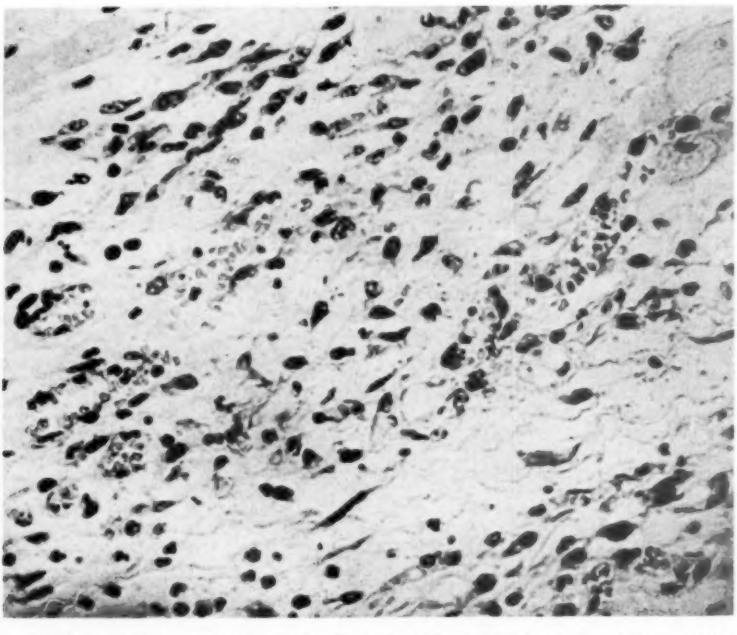

Fig. 9.—Section of the myocardium in Case 2. Hemosiderin-eosin stain x 300. Note the large endothelial cells.

DISCUSSION

It was apparent that progressive myocardial insufficiency dominated the clinical picture in the above two cases, but the etiological factors underlying the heart failure were obscure. Both cases showed clear evidence of marked cardiac enlargement, but no signs of valve disease or hypertension. In Case 2 there was no history of rheumatic infection, no evidence of syphilis, and no history of an acute infection antedating the appearance of heart failure. So far as one could tell, the patient's symptoms appeared insidiously, and in spite of treatment he went rapidly downhill to death from circulatory failure. One observes patients, usually males beyond forty, who present just such a clinical picture and who show at post-mortem extensive fibrosis of the ventricular muscle secondary to coronary arteriosclerosis. This process appeared as the most likely etiological factor in Case 2.

In Case 1, the final clinical diagnosis was even more difficult to establish. The nature of the cardiac affection ten years previously, with edema, breathlessness, and precordial pain, was obscure. This had disabled the patient for several months, but he apparently made a complete recovery. To complicate the picture further was the vague history of rheumatism at the age of 16 years. Although the clinical findings were by no means characteristic of rheumatic heart disease, yet in the light of the previous history rheumatic involvement of the myocardium seemed the most likely etiological factor, hence this clinical diagnosis was submitted.

At autopsy the hearts in the two cases were similar; they were flabby, dilated and hypertrophic, and on cut section presented clear evidence of a damaged myocardium. However, the endocardium, the valve apparatus, and the pericardium appeared normal. Histologically both hearts showed extensive inflammatory changes, chiefly in the interstitial tissue but also involving the parenchyma. The widespread muscle damage afforded an adequate explanation for the progressive circulatory failure observed during life, but a microscopic study of the myocardial lesions threw no light on the etiology of the disease. This statement of opinion is made in full appreciation of the difficulties in eliminating rheumatic infection as the etiological factor in our cases. For this reason a careful search for Aschoff nodules was made, but none were found.

It is of course conceivable, as Sacks[7] states, that diffuse infiltrations of the myocardium may represent exaggerated examples of the less conspicuous leucocytic collections which regularly accompany the Aschoff body. If this be true, then our cases as well as those previously recorded may be examples of rheumatic involvement of the myocardium, but this question—difficult either to prove or to disprove—is by no means settled, and until evidence to the contrary is established, we believe that the cases here reported belong in the group of so-called acute isolated myocarditis. To regard such cases as rheumatic would, in the light of our present knowledge, contribute nothing to the solution of the problem.

The cause of the cardiac hypertrophy in this disease is a tempting speculation. For example, the heart in Case 1 weighed 600 grams; in Case 2, 700 grams, and in the majority of the previously reported cases the heart was heavier than normal. Some authors believe that myocardial fibrosis leads to hypertrophy, and this assumption is used to explain the increased size of muscle fibers in the vicinity of infarcts. That the minimal fibrotic changes seen in our cases led to the hypertrophy found, seems a far-fetched assumption. A more reasonable explanation is that recently suggested by the work of Eyster.[8] He found in dogs that dilatation of the heart was the initial and immediate reaction to an experimental lesion. After a period of a few days, the heart returns to its normal size and hypertrophy then gradually develops, reaching a maximum for a single lesion in about eighty days. Eyster also made this significant observation; that hypertrophy ensues in spite of the fact that the experimental lesion (aortic stenosis produced by rubber-band ligatures about the root of the aorta) is removed after a few days and during the period of dilatation. It appears from Eyster's experiments that the stretching of the heart muscle from dilatation supplies the stimulus for the subsequent development of hypertrophy. On the basis of these experimental observations it is conceivable that widespread inflammatory changes in the myocardium, as found in our two cases, may lead to dilatation of the heart, and this in turn to hypertrophy.

Eyster, however, dealt with a myocardium which was not the seat of disease. The dilatation in his cases was what is referred to as passive dilatation, in which the chamber is dilated because of an absolute increase in intracardial pressure. The dilatation incident to myocardial disease is referred to as active dilatation. Here the muscle, because of inherent weakness incident to disease, permits of dilatation without the interposition of factors which raise intracardial pressure. Various observations indicate that stretching of the muscle in diastole induces hypertrophy but that this fact applies to those cases in which the muscle is the seat of concurrent degenerative disease is open to doubt. There is at least a reasonable question as to whether or not such diseased muscle is capable of the increased nutritional function which would appear to be necessary for hypertrophy to occur.

The assumption that hypertension existed at some period in the lives of these two patients might explain the hypertrophy, but would not explain the myocarditis. Furthermore, the coincidence of hypertrophy, myocarditis and dilatation in all the cases reviewed would require similar assumption of hypertension in such young individuals that it would be practically untenable.

It is unfortunate that there is no uniform terminology for the type of myocarditis here reported. Past writers use the term "interstitial," "circumscribed," "diffuse," "isolated," and "idiopathic," singly or

in combination to describe the disease. Since primary involvement of the myocardium is the most characteristic clinical and pathological feature of this disease, it seems to us that the term "isolated myocarditis," acute or subacute, is the most appropriate.

SUMMARY

The clinical and pathological observations on two cases of acute isolated myocarditis of undetermined etiology are recorded, together with a tabulation of the pertinent data in thirty similar cases previously reported.

REFERENCES

1. Aschoff, L.: Zur Myokarditisfrage, Verhandl. d. Deutsch. path. Gesellsch. **8:** 46, 1904.
2. Fiedler, A.: Ueber akute interstitielle Myokarditis. Reference in Centralbl. f. Innere Med. **21:** 212, 1900.
3. Steffen, A.: Zur akuten Myokarditis. Jahrb. f. Kinderheilk., **27:** 223, 1888.
4. Kaufmann, E.: Lehrbuch der speziellen pathologischen Anatomie, Berlin Leipzig, 1922.
5. Pal, J.: Akute, isolierte, interstitielle Herzmuskelentzündung, Wien. med. Wehnschr., **66:** 980, 1916.
6. Hafner, A.: Ueber akute, diffuse, interstitielle Myokarditis, Deutsch. Arch. f. klin. Med. **88:** 236, 1922.
7. Sacks, B.: Pathology of Rheumatic Fever, AM. HEART J. **1:** 750, 1926.
8. Eyster, J. A. E.: Cardiac Dilatation and Hypertrophy, Tr. A. Am. Physicians **42:** 15, 1927.
9. Baumgartner, H.: Ueber spezifische diffuse produktive Myokarditis, Frankfurt. Ztschr. f. Path. **18:** 91, 1916.
10. Cohn, L.: Ueber diffuse subakute Myokarditis. Inaugural Dissertation Heidelberg, 1915, cf. Kaufmann, E., Lehrbuch der speziellen pathologischen Anatomie, Berlin und Leipzig, 1922.
11. Fiebach, R.: Ueber isolierte diffuse akute Myokarditis, Virchows Arch. f. path. Anat. **233:** 57, 1921.
12. Förster, F.: Ueber Myokarditis und Gefässkrankheiten im Kindesalter, insbesondere nach akuten Infectionskrankheiten, Deutsche Arch. f. klin. Med. **85:** 35, 1905.
13. Freund, G.: Zur Kenntniss der akuten, diffusen Myokarditis, Berl. klin. Wehnschr. **35:** 1077 and 1106, 1898.
14. Gierke, E.: Ueber grannlierend-productive Myokarditis mit Regeneration von Herzmuskelfasern, Beitr. z. path. Anat. u. z. allg. Path. **69:** 72, 1921.
15. Josserand, E., and Gallavardin, L.: De L'Asystolie Progressive des Jeunes Sujets par Myocardite Subaigue Primitive, Arch. Gen. d. Med. **78:** 513 and 684, 1901.
16. Lemke, R.: Zur Frage der Primaeren akuten und parenchymatoesen Myokarditis, Virchows Arch. f. path. Anat. **248:** 345, 1924.
17. Mordre, S. K.: Acute interstitial Myocarditis, Norsk. Mag. f. Laegevidensk. **85:** 705, 1924.
18. Rindfleisch, W.: Ein Fall von diffuser akuter Myokarditis, Inaugural-Dissertation, Koenigsberg, 1898.
19. Saltykow, S.: Ueber diffuse Myokarditis, Virchows Arch. f. path. Anat. **182:** 1, 1905.
20. Schilling: Zwei Fälle von akuter, idiopathischer Myokarditis mit zahlreichen Riesenzellen, Verhandl. d. deutsch. path. Gesellsch. **18:** 227, 1921.
21. Schmincke, M.: Izolierte akute diffuse interstitielle Myokarditis, Deutsche med. Wchnschr. **47:** 1047, 1921.
22. Selletin, L.: Akute isolierte interstitielle Myokarditis, Ztschr. f. klin. Med. **56:** 298, 1904.
23. Stolz, E.: Ueber die Aetiologie und die Folgen der isolierten diffusen interstitiellen Myokarditis, Zentralbl. f. Herz-u. Gefässkr. **15:** 183, 1923.
24. Wolf: Ein Fall von Myokarditis akute. Inaugural Dissertation, Muenchen, 1896. cf. Kaufmann, E., Lehrbuch der Speziell, Pathologischen Anatomie. Berlin und Leipzig, 1922.
25. Zuppinger: Ueber Herztod bei anscheinend bedeutungslosen oberflaechl. Geschwuersprozessen, Wien. klin. Wchnschr. **34:** 799, 1901.

STUDY OF THE R-T INTERVAL IN MYOCARDIAL INFARCTION*

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CORONARY occlusion with myocardial infarction has come to be considered a distinct clinical entity, the diagnosis of which can be made during life with a high degree of certainty. The first combined clinical and electrocardiographic observations following acute coronary occlusion were reported by Herrick. The electrocardiogram, taken forty-three days after the occlusion, and published by him (Fig. 1), showed relatively late changes in the R-T interval following infarction of the myocardium in the region supplied by the anterior descending

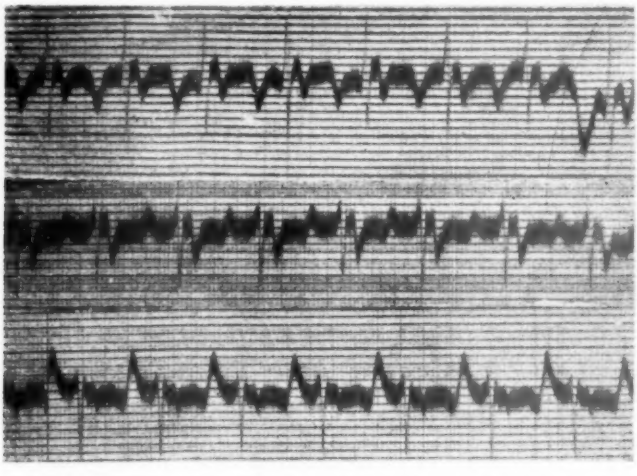

Fig. 1.—Electrocardiogram taken May 3, 1917, forty-one days after the symptoms of coronary obstruction. Digitalis not used at this time. (From Herrick.)

branch of the left coronary artery. This tracing is a classical example of the T_1 type of changes which will be described later in this paper. At the end of his article Herrick made this rather prophetic statement: "The thought has been that if it can be proved that with a certain artery obstructed there is a definite lesion in the heart-muscle or in the conducting system, and if with that lesion there is a definite electrocardiogram, may we not, when we encounter that abnormal electrocardiogram in the human being, particularly if he has had symptoms suggestive of coronary thrombosis, be able to state with a reasonable degree

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of certainty that the patient has had obstruction in a particular portion of the coronary system? May it perhaps be possible to localize a lesion in the coronary system with an accuracy comparable to that with which we locate obstructive lesions in the cerebral arteries?''

Smith reported alterations of the T-waves and of the R-T segment occurring more or less constantly after ligation of the branches of the left coronary artery in dogs and mentioned that similar changes in man were to be observed in the case reported by Herrick. Pardee[9] observed

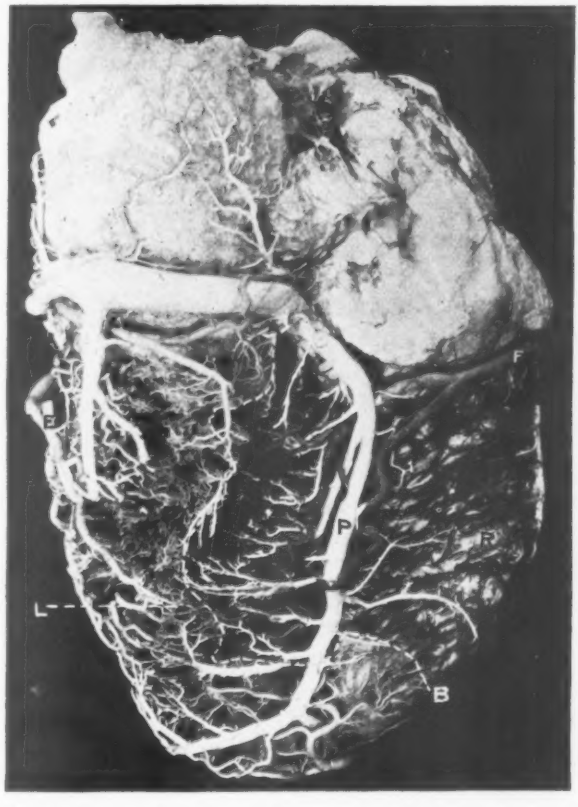


Fig. 2.—Posterior view, after preparation by celluloid-corrosion method, of heart from a man forty-two years old. *R*, right ventricle; *L*, left ventricle; *E*, left coronary artery; *F*, right coronary artery; *P*, posterior interventricular vein; *A—B*, line separating the portions of the heart supplied by the right and left coronary arteries. This represents almost the average normal line of separation except in the base of the left ventricle where the circumflex branch of the left coronary artery supplies a little more of the posterior surface than is usual.

and described in man a type of deformity of the R-T segment such as Smith had obtained in dogs following ligation of branches of the left coronary artery and designated this the coronary T-wave.

Many observers have contributed electrocardiographic tracings in man corroborating the observations of Smith and Pardee.[9] In a recent excellent contribution Parkinson and Bedford reported the electrocardiographic changes occurring in twenty-eight cases following infarc-

tion. They have extended our knowledge of the variations in the changes of the R-T segment associated with infarction and have suggested the classification of these variations into two main types.

A thorough knowledge of the distribution of the coronary arteries is of paramount significance in any attempt to interpret the electrocardiographic changes occurring in myocardial infarction. Therefore it seems advisable to emphasize certain observations on the blood supply of the heart before proceeding further in this study. The anatomical data which we present were obtained from a study of hearts of human beings injected by the celluloid and corrosion method, which Whitten has described.

Spalteholz, Gross and others have emphasized that there is considerable variation in the coronary circulation in normal hearts. The supply of the posterior surface of the left ventricle probably is most variable, and a detailed knowledge of the variations in the blood supply of this region is of the greatest importance for reasons which will become obvious.

The right coronary artery enters the coronary sulcus shortly after it takes origin from the aorta. Continuing in this groove, which lies at the juncture of the right auricle and the right ventricle, it passes to the posterior surface of the heart. As it goes around the right side of the heart, branches are given off at intervals, and these generally course in the direction of the apex. At the point where the right coronary artery crosses the posterior interventricular sulcus, it gives off a large branch, the posterior descending artery (Fig. 2). The latter vessel generally extends down the posterior interventricular sulcus from two-thirds to three-fourths of the distance from the coronary sulcus to the apex. This artery supplies approximately the posterior third of the interventricular septum. At the point of origin of the posterior descending artery, the right coronary artery generally crosses the posterior interventricular sulcus to reach the posterior surface of the left ventricle. Here the right coronary artery usually divides into two or three branches, which, turning rather sharply, course about three-fifths of the distance from the coronary sulcus to the apex. These vessels usually do not extend to the left beyond a line midway between the posterior interventricular sulcus and the obtuse or left margin of the heart.

There are two definite variations from the average normal right coronary artery. Sometimes the posterior descending artery and the branches of the right coronary artery which reach the posterior surface of the left ventricle extend to the apex and occasionally slightly beyond this point (Fig. 3). In this case, the right coronary artery supplies practically the whole posterior surface of the left ventricle, a portion or all of the apex, as well as the posterior third of the interventricular septum.

At times, the right coronary artery is relatively unimportant and

does not reach the posterior interventricular sulcus or the posterior surface of the left ventricle. In that event it is evident that the left coronary artery must supply the entire posterior portion of the left ventricle as well as the whole interventricular septum (Fig. 4). This is accomplished by the circumflex branch of the left coronary artery, which becomes of unusual importance, and proceeds along the base of the left ventricle, at the level of the atrioventricular juncture, finally to reach the posterior interventricular sulcus down which it courses

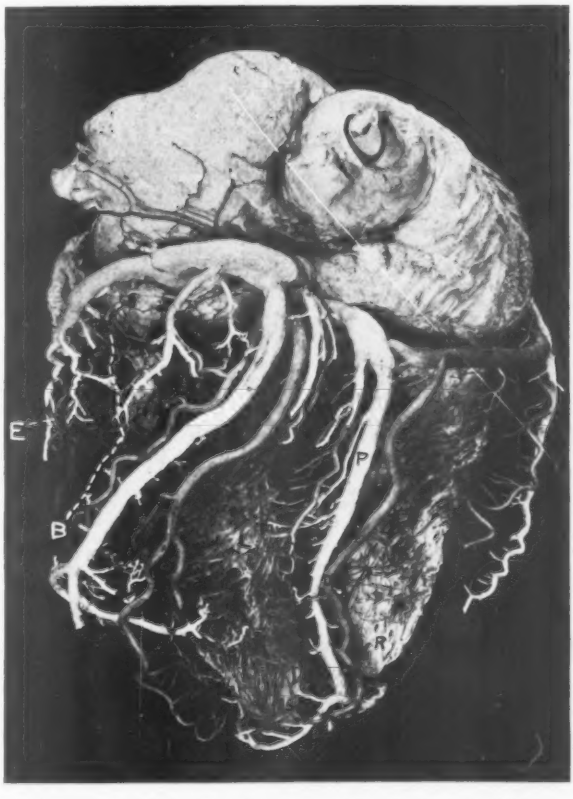


Fig. 3.—Posterior view of heart after preparation by celluloid-corrosion method. The right coronary artery supplies the entire posterior surface of the left ventricle and the apex. *R*, right ventricle; *L*, left ventricle; *P*, posterior interventricular vein; *D*, posterior descending artery (right coronary); *A—B*, line of separation of parts of left ventricle supplied by right and left coronary arteries; *E*, left coronary artery; *F*, right coronary artery.

toward the apex to become the posterior descending (or interventricular) artery.

The left coronary artery is generally considered to have two main branches. The largest, the anterior descending artery, proceeds down the anterior interventricular sulcus to the apex, and from this point it generally extends on to the posterior surface of the heart, coursing up the posterior interventricular sulcus usually from a fourth to a third of

the distance toward the base of the ventricles. As the artery passes down the anterior surface of the heart, it gives off large branches to supply the anterior surface of the left ventricle and the anterior two-thirds of the interventricular septum, but it gives only a few small vessels to supply the anterior surface of the right ventricle.

The other main division of the left coronary artery is known as its circumflex branch. It arises near the origin of the left coronary artery and courses immediately to the left, following the coronary sulcus for a variable distance. It generally passes around the obtuse or left margin

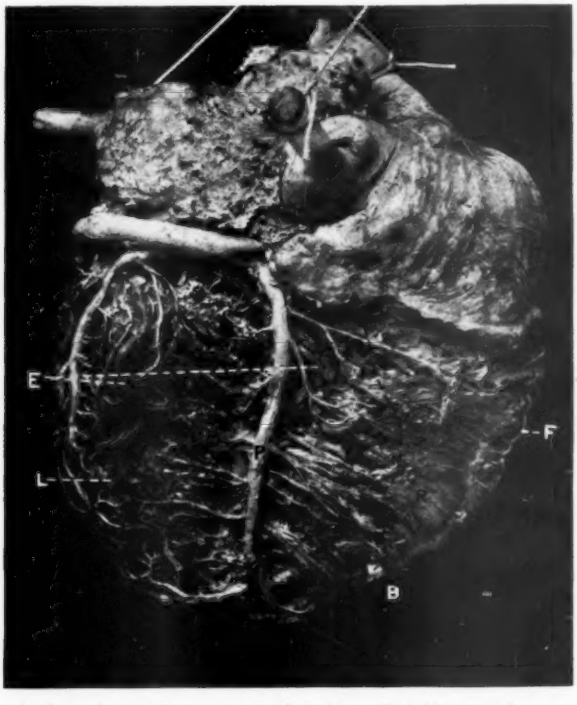


Fig. 4.—Posterior view, after preparation by celluloid-corrosion method, of heart from a woman fifty-five years old. The left coronary artery supplies the entire posterior surface of the left ventricle and a portion of the posterior surface of the right ventricle. *R*, right ventricle; *L*, left ventricle; *P*, posterior interventricular vein. *A—B*, line of separation of portions of right ventricle supplied by right and left coronary arteries; *E*, left coronary artery; *F*, right coronary artery.

of the heart to reach and supply the left third or half of the posterior surface of the basal three-fifths of the left ventricle. That this artery occasionally assumes additional significance and extends to the posterior interventricular sulcus has been mentioned in the discussion of the variations of the right coronary artery.

In the average normal heart the left coronary artery supplies the entire anterior surface of the left ventricle, the adjacent third of the anterior surface of the right ventricle, the apex of both ventricles, all of the interventricular septum at the apex, the anterior two-thirds of

the septum above that point, and the left half of the posterior surface of the left ventricle. The right coronary artery usually supplies two-thirds of the anterior surface and all of the posterior surface of the right ventricle with the exception of the apex. It also generally supplies the posterior third of the interventricular septum (except at the apex), and the adjacent half of the basal three-fifths of the posterior surface of the left ventricle.

In a separate article one of us (Whitten[16]) has shown a vast difference between the branches of the right coronary artery supplying the right ventricle, and the branches of the right and left coronary arteries supplying the left ventricle. These arteries supplying the right ventricle appear to spread out over the heart in the same general plane as the subdivisions of the artery from which they arise. The wall of the left ventricle is much thicker than that of the right. The branches which supply the former, whether they originate from the right or the left coronary artery, course along the surface of the heart just beneath the epicardium. Their branches do not spread out in the same general plane. Instead, they leave at right angles and penetrate straight through the myocardium, giving off very few branches until they reach the endocardium where they again turn at a sharp angle and end in a mass of fine arterioles.

The left coronary artery is immobilized to a considerable degree by these branches which penetrate the myocardium at right angles. The smaller branches of the right coronary artery, which supply the right ventricle, do not possess any conspicuous deep branches. On the contrary, the main branches which supply the posterior interventricular septum and posterior portion of the left ventricle are immobilized in a manner similar to that in which the branches of the left coronary artery are immobilized. In its first portion, the right coronary artery has much greater mobility than the left. It seems reasonable to believe that the architecture of the branches of the left and right coronary arteries is significant in the occurrence of occlusion in these vessels and, furthermore, suggests a reason why occlusion of the right coronary artery is manifested chiefly by infarction in the posterior portion of the left ventricle.

The anterior descending branch of the left coronary artery courses straight except for the tortuosities that occur with increasing age. As this vessel is anchored securely by deep vessels passing into the septum, the tortuosities often become marked. The right coronary artery, while crossing the right side of the heart, swings in an arc making a complete semicircle. If this vessel becomes sclerosed, it does not become very tortuous because it is free to project farther from the surface of the heart and simply swings around in a larger arc. It is suggested that this is a protection to this part of the right coronary artery.

It is possible that other anatomical factors, such as anastomosis or

the thebesian circulation, also may render the right ventricle more or less immune to infarction.

Myocardial infarction may be acute or chronic, or acute infarction may be superimposed on chronic infarction. Acute infarction results from sudden, complete occlusion of a coronary artery or one of its branches. Following this over a long period, fibrous tissue gradually replaces the infarcted muscle fibers to an extent which will depend largely on the effectiveness of anastomotic circulation in that region. This end stage of acute infarction is often difficult to distinguish from the chronic type which results from the gradual, almost complete obliteration of the lumen of a coronary vessel that goes to a particular region, although in chronic infarction the fibrosis is more likely to assume a more patchy distribution. It seems probable that gradually developing chronic infarction may not be signalized by dramatic events, with severe pain, such as are seen in acute infarction. It is even probable that it may occur with little if any pain, judging from our clinical records. We agree with Pardee that it is probable that chronic infarction, provided it produces focal rather than diffuse change, is capable of bringing about the typical alteration of the R-T segment seen in acute myocardial infarction.

The criteria for the recognition of changes in the electrocardiogram indicative of myocardial infarction have been established fairly well. Pardee, in 1920, called attention to these changes in clinical electrocardiograms and in 1925 amplified these observations. He stated that the characteristics of the electrocardiogram in myocardial infarction were the presence in one or more leads, usually only in one, of a downward, sharply peaked T-wave with an upward convexity of the S-T or R-T interval. When this change in the T-wave occurred in the third lead only, he considered that the change was not significant, unless the T-wave was inverted in Lead II, although convexity of the segment preceding the T-wave in Lead II need not be present. In his original description he pointed out that the T-wave does not start from the zero level, that it quickly turns away from its starting point in a sharp curve and ends in a sharply peaked T-wave somewhat larger than normal.

Parkinson and Bedford have contributed much to the criteria of recognition of the changes in the R-T interval in infarction.* They found, as did Pardee, that the R-T segment arose below or above the isoelectric line, best seen in Leads I and III and occurred "constantly in opposite directions in these two leads; thus an R-T elevation in Lead I is associated with an S-T depression in Lead III and vice versa." However, they found that an R-T deviation may be found in a single lead or in combined Leads I and II, or II and III in which case the deviation

*Hereafter in this paper the designation R-T will be used to include the segment between the QRS complex and the end of the T-wave. At times this will actually be the S-T segment.

was in the same direction in the two leads. They recognized various contours of the R-T interval; it may be a flat-topped plateau, descending gradually to the iso-electric level; it may rise gradually, reaching a summit at the end of the plateau, or it may form a dome-shaped elevation at the end of which the peak of a negative T-wave may occur. These authors emphasized that when R-T deviation was marked, T-waves, strictly speaking, were not evident. They pointed out that in these cases the T-waves approximated the monophasic type. The R-T deviation was transient and usually when repeated electrograms were made, was disappearing before the negativity of the T-wave was well developed.

Parkinson and Bedford further divided the curves into types T_1 and T_3, types depending on whether the T-waves were inverted in Lead I or in Lead III. Differing from Pardee, they concluded that a sharply pointed, inverted T-wave in Lead III "may be the only relic of a previous cardiac infarction." Although we have no case in which we can obtain positive evidence on this point, we believe that it is probably a justifiable conclusion.

In interpreting electrocardiograms of infarction it is of the utmost importance to know the time they were taken in relation to the time when the infarction probably occurred. In the first week after infarction change of level and contour of the R-T segment is likely to occur, and frank inversion of the T-wave often is seen only after this. Multiple electrocardiograms often enable one to identify changes in the R-T segment that are indicative of infarction and that are not clearly shown in a single tracing. A careful inspection of the changes in the R-T interval in Lead II, particularly with the purpose of determining to which of the two other leads it bears the closest resemblance, will furnish the safest guide to the classification into types T_1 and T_3. Thus, the elevation and rounding of contour of the R-T segment in Leads I and II will serve to identify the abnormality as of type T_1, although no inversion of the T-waves is present; the same phenomena in Leads II and III will place the tracing in the group T_3. Occasionally in Lead I the identification of an abnormality of type T_1 depends on an inverted T-wave in that lead, with R-T characteristics preceding it which suggest infarction. We have not encountered any instance in which we could unquestionably place a tracing in the type T_3 on the basis of R-T changes in Lead III unattended by somewhat similar changes occurring in Lead II. All degrees of bundle-branch block must be carefully excluded before an electrocardiographic tracing may be said to be characteristic of myocardial infarction. Care must be exercised in interpreting changes in the R-T interval in electrocardiograms which give evidence of auricular fibrillation. Furthermore, certain cases of hypertension will cause changes in the level of the R-T

interval which closely simulate the late changes in the electrocardiogram following infarction.

In recapitulation, the early changes (first week) following infarction are elevation of the R-T interval above the iso-electric line; a convex, dome-shaped, or sloping R-T segment; the tendency of changes in level to be in opposing directions in Leads I and III, and in Lead II an appearance of the R-T segment simulating more or less closely those in Lead I or Lead III. In this early stage inversion of the T-wave often is absent or at most is diphasic in type. At a later stage, frank inversions of the T-waves appear and the T-waves are likely to be deep, abrupt and rather sharply peaked. In the reciprocal lead (Leads I and III act in a reciprocal manner) the T-wave is likely to become more positive, abrupt in ascent, and sharply peaked. At this stage, the R-T interval tends to return or does return to the iso-electric level. It is at this stage that the upward convexity of the R-T segment, preceding the sharply peaked inverted T-wave, presents the picture described by Pardee[9] as the "coronary T-wave."

In the light of these observations we have classified our electrocardiograms into types T_1 and T_3 and have subdivided these types into groups listed as typical, less typical, probable and indeterminate. That we cannot classify more of the tracings as typical is due to the fact that in many cases only a single electrocardiogram was taken and to the further fact that single or multiple electrocardiograms were taken in some cases at a long or indeterminate interval after infarction. Electrocardiograms obtained in cases of infarctions of about equal duration, in both the anterior and posterior portions of the left ventricle, may be difficult to classify into types T_1 or T_3.

Few reports of cases in the literature include a definite description of the site of infarction, an accurate study of the circulation in relation to the infarcted portion and the electrocardiographic tracings. Forty-seven cases in which necropsy was done at The Mayo Clinic, and in which inversion of the T-wave or alterations in the R-T interval were present, were studied. In these cases, the exact site of the infarction was observed especially with reference to the blood supply from the right or the left coronary artery. Of the forty-seven cases, twelve are selected for detailed report.

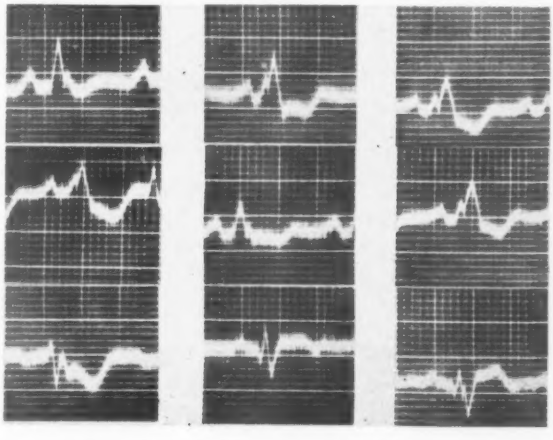
REPORT OF CASES

CASE 1.—A man, 57 years old, had complained of shortness of breath for seventeen months before he was first seen as a patient. Twenty-seven days before the first electrocardiogram was taken he had been seized with a feeling of pressure in his chest and had experienced much difficulty in breathing while driving his car. He had had to be helped to bed, had remained there three days, and two days more had passed before he had been able to walk about. After this, dyspnea had greatly increased. The blood pressure, measured in millimeters of mercury, was 130 systolic and 90 diastolic. In the first electrocardiogram there were inverted

T-waves in Leads II and III, suggestive of coronary occlusion. There was depression of the R-T interval in Lead I. The QRS interval was 0.12 second.

On the day of admission to the hospital the patient was unconscious for three or four minutes, and over the precordium he had heavy pressing pains which radiated into both arms. He was cold and clammy, and afterward became very weak. The following day there was a depressed R-T plateau in Leads I and II, with elevation of the plateau in Lead III. The T-wave appeared diphasic in all leads. Two days later, the R-T plateau had deepened in Leads I and II and had risen in Lead III. The QRS interval was 0.12 second. Although it was difficult to identify the T-wave with certainty, it appeared to be diphasic. The first electrocardiogram is of type T_2 and the last two tracings are of type T_1 (Fig. 5).

At necropsy an old infarct was found in the posterior surface of the left ventricle, in the area supplied by the right coronary artery. In the anterior surface of the left ventricle, in a region supplied by the anterior descending branch of the left coronary artery, there was a recent infarct.



A *B* *C*

Fig. 5.—Case 1. *A*, incomplete left bundle-branch block following infarction of the posterior portion of the left ventricle. The QRS interval is 0.12 second. *B*, incomplete right bundle-branch block one day after infarction in the anterior portion of the left ventricle; *C*, three days following infarction in the anterior portion of the left ventricle.

The history establishes accurately the time of occurrence of the two infarctions. The first electrocardiogram is associated with infarction in the posterior part of the left ventricle, whereas the last two are associated with infarction in the anterior portion of the left ventricle. The shift from an incomplete left bundle-branch block to an incomplete right bundle-branch block following the second infarction is significant. This case furnishes an explanation for electrocardiograms in which shifts in the type of changes in the T-wave occur and suggests that when such a shift is observed one must suspect the occurrence of infarction in a region of the left ventricle supplied by one coronary artery, together with preexisting infarction in a region supplied by the other coronary artery. This interpretation carries further weight if it is supported by a history of separate attacks indicative of coronary

occlusion, such as was obtained in this case. It is impossible to state the relative significance of infarction and bundle-branch disturbance in determining the contour and direction of the R-T intervals in this case.

CASE 2.—A man, 80 years old, came under observation because of an oppressive sensation in the chest, radiating to the left shoulder, which had begun about twelve hours previous to admission. He had been subject to attacks of paroxysmal dyspnea for eight years and to periods of oppression in the chest for four years.

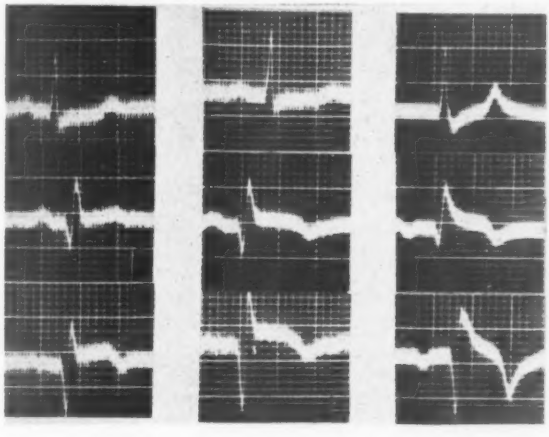
Fig. 6.—Case 2. *A*, recent infarction of the posterior portion of the left ventricle adjacent to the posterior interventricular septum; *B*, portion of posterior part of left ventricle folded back.

He became rapidly worse soon after admission to the hospital, leucocytosis and fever developed, and there was a fall in blood pressure from 110 systolic and 80 diastolic to 84 systolic and 52 diastolic. He died on the fourth day after admission.

At necropsy infarction involving most of the posterior surface of the wall of the left ventricle, the posterior portion of the interventricular septum, and one of the papillary muscles, was found (Figs. 6 and 7). This was shown to be due to occlusion of the right coronary artery. Purulent adhesive pericarditis was present.

Three normal electrocardiograms had been taken two and four years before the patient was admitted to the hospital. On the day of admission, there was a diphasic T-wave in Lead I, with depression of the S-T interval, and upright T-waves in Leads II and III, with elevation of the R-T interval. On the next day, the T-wave in Lead I became upright, but depression of the S-T interval remained. In Leads II and III, the T-wave had become inverted and the R-T interval had become an elevated plateau which arose high on the right limb of the wave. Similar but even more typical electrocardiographic changes of type T_3 were observed on the two following days.

CASE 3.—A man, 67 years old, had complained of attacks of precordial pain for fifteen years. He was admitted May 1, 1926, with a severe attack of precordial pain; the character of which, together with the results of physical examination,



A *B* *C*

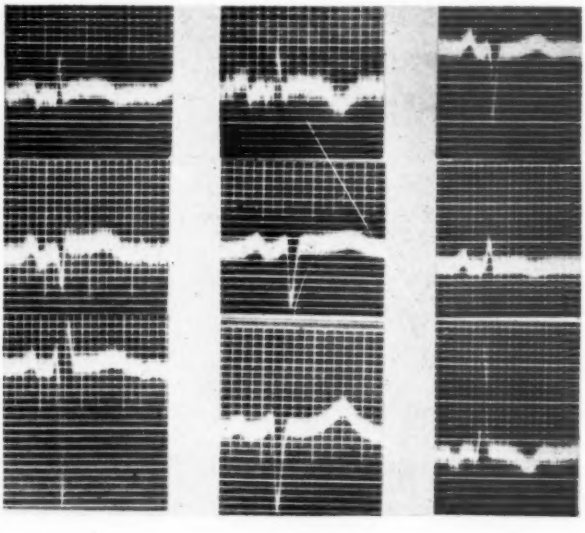
Fig. 7.—Case 2. Typical electrocardiogram of type T_3. *A*, an electrocardiogram made one day following the infarction in the posterior portion of the left ventricle that is shown in Fig. 6; the R-T interval is elevated in Leads II and III, and the S-T interval is depressed in Lead I. *B*, two days after infarction. *C*, three days after infarction; the origin of the R-T interval is high in Leads II and III; there is an abrupt, sharp, deep inversion of the T-wave in Lead III, and a sharp, high, positive T-wave in Lead I.

left no doubt but that we were dealing with a case of coronary occlusion with myocardial infarction. The blood pressure, which had been 130 systolic and 78 diastolic, now dropped to 95 systolic and 60 diastolic. From the third to the ninth day after infarction had occurred, the T-wave in Leads I and II became more positive and crescentic in contour; there was a gradual rise from the S-wave to the T-wave. Ten days after the infarction, the T-wave in Lead I was inverted, with a rounded, slightly positive wave preceding the T-wave; this contour frequently is seen preceding inversion of the T-wave in coronary occlusion (Fig. 8). At intervals of nineteen, twenty-one, twenty-four, twenty-six and forty-eight days after the coronary occlusion, the T-wave was inverted in Lead I. All of these tracings gave evidence of marked left ventricular preponderance. Two tracings, taken before the occlusion occurred, contained positive T-waves in all leads.

June 29, 1926, the patient had a second severe attack of precordial pain which lasted eight hours. Coronary occlusion was suspected but the evidence for it was

not conclusive. After eight days, he left the hospital. Tracings taken August 23, and 28, gave evidence of definite right ventricular preponderance with inversions of the T-wave in Leads II and III (Fig. 8). August 25, 1927, the patient was seized with a severe attack of precordial pain which lasted one day and which was indicative of myocardial infarction. Death occurred from progressive heart failure. Electrocardiograms taken at this time were unsatisfactory for technical reasons, and a positive opinion about the changes in the T-wave cannot be advanced.

There was sclerosis of the right coronary artery, graded 2. The anterior descending branch of the left coronary artery was markedly sclerosed, and its lower one-third was occluded. Infarction of the lower one-third of the anterior surface of the left ventricle and of the adjacent portion of the interventricular septum was found. There was marked thinning of the anterior and apical portion of the left ventricle,



A *B* *C*

Fig. 8.—Case 3. Electrocardiogram of type T_1 shifting to a less typical type T_3 in a case of old infarction in the apex and the anterior portion of the left ventricle. There was more recent infarction in the posterior surface of the left ventricle. *A*, tracing made ten days after first infarction; there is an elevated S-T interval in Leads I and II, with an upward convexity of the S-T interval. *B*, the features are the same as in *A* except for deeper inversion of the T-wave in Lead I, with typical reciprocal rise of the T-wave in Lead III; this electrocardiogram was made nineteen days after the first infarction. *C*, tracing made seven weeks after the second infarction; T waves are inverted in Leads II and III.

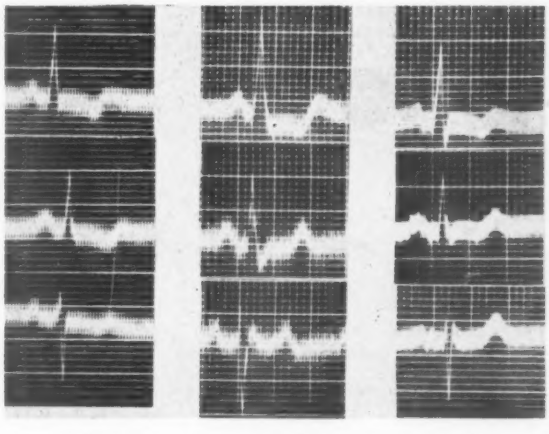
with an organized thrombus beneath this area. A region of healed pericarditis completely obliterated the pericardial sac; this probably was related to the history of pericarditis in childhood.

On the posterior surface of the heart, adjacent to the septum, midway between the apex and base, was an area about 5 by 4 cm., which in a tangential section had a distinctly yellowish cast but in which gross fibrosis was not present. A microscopic section taken from this region immediately adjacent to the septum showed that this area was undergoing infarction, with destruction of muscle fibers, with cellular infiltration and with practically no replacement by fibrous tissue. This was obviously a more recent infaret than the one at the apex, where the muscle fibers were practically all replaced by fibrous tissue. The infarction of the posterior basal portion of the left ventricle did not appear to have been acute, and it may

have occurred as long previously as June 29, 1926. If so, it would furnish a satisfactory explanation of the inversions of the T-wave in Leads II and III. The R-T interval in Lead III in these tracings had a rounded convexity somewhat suggestive of myocardial infarction.

CASE 4.—A man, 54 years old, had experienced substernal burning on exertion for seven years. Two and a half months before admission the patient had had an attack of substernal pain radiating down the left arm; pulmonary edema had appeared at this time. A similar attack had occurred three weeks later. The blood pressure at examination was 158 systolic and 112 diastolic.

At necropsy, sclerosis, graded 2, was found in the right coronary artery. In the left coronary artery sclerosis, graded 3, was found and the main trunk was occluded. There was chronic, diffuse fibrosis involving the anterior two-thirds of the left ventricle and the anterior half of the lower two-thirds of the interventricular



A *B* *C*

Fig. 9.—Case 4. Electrocardiogram made two-and-a-half months after infarction in the anterior portion of the left ventricle. *A*, there is a downward sloping R-T segment in Leads I and II and inverted T-waves in Leads I and II. *B*, four days later; there are depressed R-T segments in Leads I and II, and T-wave, in Lead I is diphasic. *C*, twenty-three days after tracing *A* was made: the tracing is the same as that in *B*; a sharply peaked, high T-wave has developed in Lead III.

septum. Fibrosis was found at the apex and in the adjacent posterior portion of the left ventricle. There was no fibrosis in the area supplied by the right coronary artery.

The electrocardiogram taken the day of admission revealed inverted T-waves in Leads I and II with a downward sloping R-T interval in both leads. A tracing taken five days later disclosed upright T-waves in Lead II, although the R-T interval in that lead still had its origin below the iso-electric level. Essentially the same type of tracing was obtained twenty-three days after admission (Fig. 9). The T-wave in Lead III had a tendency to become more positive and more sharply peaked. The modifications of the R-T intervals observed here are sufficient to cause this tracing to be classified with those showing late changes of type T_1.

CASE 5.—A man, 58 years old, had an attack of acute dyspnea seven months before coming to the clinic following a heavy meal. There was a history of rheumatic fever at fifteen years of age, with an attack of pericarditis at that time, and of another attack at the age of twenty years. The patient had not complained of pain in the chest. At examination, the heart measured 21.5 cm. in its greatest transverse diameter, and there was a short to-and-fro murmur at the aortic area. The liver was markedly enlarged, and there was edema of the lower extremities. The blood pressure was 130 systolic and 70 diastolic. Death occurred suddenly while the patient was under treatment.

Midventricular infarct was observed anterior to the obtuse margin of the left ventricle. Dissection revealed that this region was supplied by terminal branches of the circumflex division of the left coronary artery or by the branches of the accessory anterior descending artery.

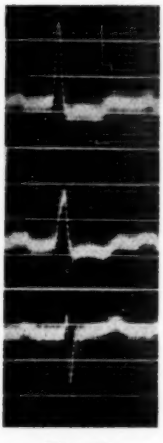


Fig. 10.

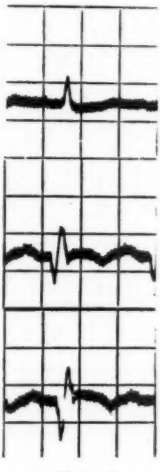


Fig. 11.

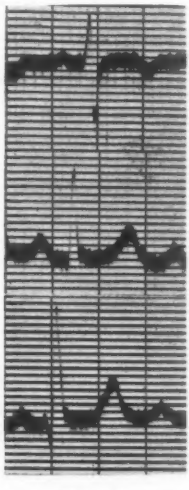


Fig. 12.

Fig. 10.—Case 5. The history suggested that infarction had occurred seven months before admission. There was old infarction in the anterior portion of the left ventricle. There are depression and slight upward convexity of the R-T interval in Leads I and II and diphasic T-waves in Leads I and II.

Fig. 11.—Case 6. Electrocardiogram made twenty days after the first attack suggesting infarction. There was infarction in the posterior surface of the left ventricle. The R-T interval in Leads II and III has a typical high origin and upward convexity.

Fig. 12.—Case 7. Electrocardiogram made in a case of old infarction in the anterior portion of the left ventricle. There is upward convexity of the S-T interval in Lead I, and high, sharply peaked positive T-waves in Leads II and III. This is a good example of the late type T_L.

In the electrocardiogram, taken twelve days before death, there was depression of the R-T level in Leads I and II, with diphasic T-waves in those leads. Slight rounding of the R-T interval was noted in each of these two leads. The contour and level of the R-T segment in Lead III appeared normal (Fig. 10).

CASE 6.—A man, 56 years old, had a severe attack of anginal pain, Nov. 24, 1927. The pain lasted for twelve hours, and morphine was required for relief. Dec. 3, 1927, the patient had another severe attack, this time with epigastric pain. He was taken to the hospital Dec. 6. At that time the blood pressure was 140 systolic and 90 diastolic. He died Dec. 25, 1927.

Necropsy revealed an acute infarct of the lower two-thirds of the posterior portion of the left ventricle, as well as infarction of the lower half of the posterior portion of the interventricular septum. There was considerable thinning of the posterior surface of the left ventricle. There was a small zone of infarction in the right ventricle, in a region closely adjacent to the posterior interventricular septum. The orifice of the right coronary artery was completely plugged by a thrombus which protruded from its orifice. In this particular case the right coronary artery supplied the posterior surface of the left ventricle as far to the left as the left or obtuse margin of the heart and extended inferiorly to the apex, as in Fig. 3. The infarcted areas were limited to the portion of the heart supplied by the right coronary artery.

The electrocardiogram, taken Dec. 13, disclosed inversion of the T-waves in Leads II and III, with the typical high origin and rounding of the R-T plateau seen in myocardial infarction (Fig. 11).

CASE 7.—A man, 77 years old, came to the clinic because of incontinence of urine which proved to be due to carcinoma of the prostate. There was no history indicative of myocardial insufficiency, although the heart was moderately enlarged. The blood pressure was 154 systolic and 82 diastolic. Death followed suprapubic cystostomy for drainage of the bladder.

At necropsy there was a fairly well localized area of diffuse fibrosis in the anterior portion of the left ventricle and adjacent septum in the apical two-thirds of the heart. This region was found to be just distal to an area of calcification in the upper third of the anterior descending branch of the left coronary artery.

The electrocardiogram taken eleven days before death contained an inverted T-wave in Lead I, with slight upward convexity of the R-T segment (Fig. 12). There was no history indicating acute infarction of the myocardium, and the appearance of the infarcted region suggested that the infarction may have occurred gradually.

CASE 8.—A woman, 64 years old, gave a history suggestive of angina pectoris of four or five years duration. Nov. 24, 1927, she had suffered from severe epigastric and precordial pain radiating down the left arm and was admitted to the hospital on the following day. At that time her blood pressure was 158 systolic and 86 diastolic. She became worse rapidly and died Nov. 30, 1927.

At necropsy, infarction was found involving the posterior surface of the left ventricle near the base. Regions of infarction also were discovered along the posterior interventricular sulcus, on what appeared to be the adjacent surfaces of the right and left ventricles; however, it was found that the posterior portion of the interventricular septum was abnormally placed, so that it encroached on the surface of the right ventricle. Consequently the region of infarction was practically confined to the posterior surface of the left ventricle and the adjacent part of the interventricular septum. The infarction was limited to the portion of the heart supplied by the right coronary artery.

The heart and vessels were injected with celloidin. Although there was some sclerosis of the left coronary artery, it could be seen that on the whole it was fairly well preserved (Fig. 13). The zone of infarction was shown by the areas in which blood vessels were not injected. It was also observed that the right coronary artery, although it had anastomotic connections with the left coronary artery through the abnormally situated interventricular septum, was not of sufficient caliber to nourish adequately the region which it supplied.

In the electrocardiogram taken two days after the patient's severe attack of angina pectoris, there was inversion of the T-wave in Leads II and III; also, the R-T interval took origin above the iso-electric level, and there was a tendency to convexity of the plateau preceding the T-wave. In Lead I, the R-T segment tended to originate slightly below the iso-electric level. The tracing on the second day following, exhibited the same characteristics, with minor variations. The R-T segment in Leads II and III was typical of that seen in myocardial infarction (Fig. 14). Death occurred two days after the last electrocardiogram was obtained.

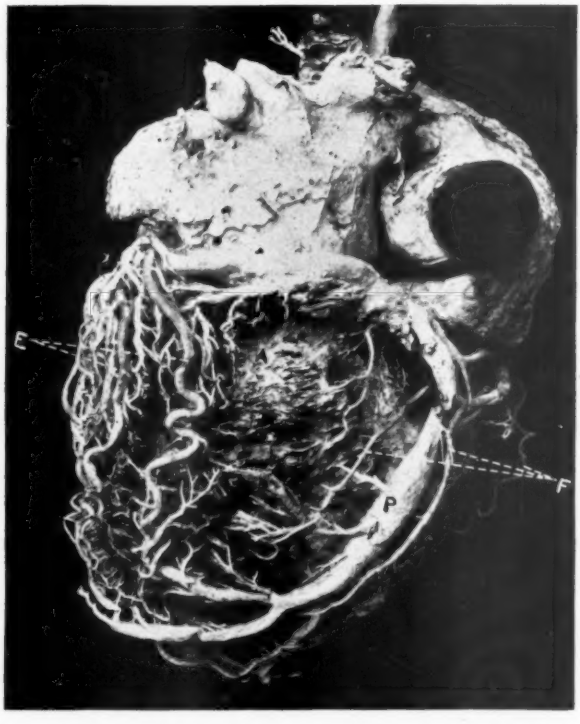


Fig. 13.—Case 8. Preparation, by celluloid-corrosion method, of a heart injected following occlusion of the right coronary artery. *A*, posterior surface of left ventricle in the region of infarction, showing the failure of the branches of the right coronary artery to be injected. *F*, branches of the right coronary artery; *E*, branches of the left coronary artery.

Case 9.—A man, 46 years old, had experienced much dyspnea following an acute respiratory infection one year before admission. During this year there had been varying degrees of cardiac decompensation, at one time requiring abdominal paracentesis. There was no history of pain in the chest. On entrance to the hospital, the patient presented the typical characteristics of marked cardiac decompensation. The blood pressure was 170 systolic and 130 diastolic. The patient failed to respond to usual measures. Death occurred from mesenteric thrombosis twelve days after admission.

At necropsy the apex of the heart was found to be the site of an old infarct, chiefly the aspect of the apex involving the posterior interventricular septum. An-

other old infarct was found 2 cm. from the base, at the juncture of the anterior interventricular septum and the anterior portion of the left ventricle, and measuring about 1 cm. in diameter. There was recent acute infarction in the posterior surface of the left ventricle and septum, extending from a point midway between the base and apex to within 1 cm. of the apex. Beneath this infarct, in its apical portion, a mural thrombus was found. This region of acute infarction, as well as the chronic infarction at the apex, was found to be in the distribution of the posterior descending branch of the right coronary artery.

Electrocardiograms were taken one and four days after admission. In the first tracing, the R-T interval was slightly depressed and ended in a diphasic T-wave in Lead I. In Leads II and III the R-T interval came off above the iso-electric level and the T-wave rose gradually to end in a summit. In the second tracing, the R-T level in Lead I was

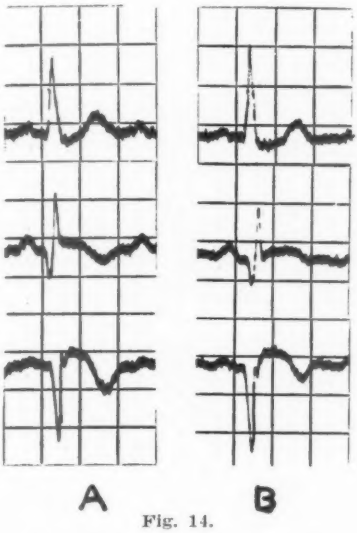


Fig. 14.

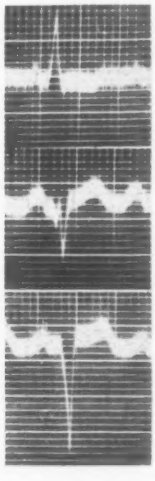


Fig. 15.

Fig. 14.—Case 8. *A*, electrocardiogram made two days after occlusion of the right coronary artery. There was infarction in the posterior surface of the left ventricle. The R-T interval is elevated in Leads II and III and the S-T interval is depressed in Lead I. *B*, electrocadiogram made four days after occlusion. The S-T interval in Leads II and III shows more pronounced upward convexity.

Fig. 15.—Case 9. Electrocardiogram made in a case of recent acute infarction in the posterior portion of the left ventricle. The R-T segment is slightly depressed in Lead I and slightly elevated in Leads II and III.

depressed and ended in an inverted T-wave. The elevation of the R-T segment in Lead II was less than in the first tracing and the peak of the T-wave was not so high. The elevation of the R-T interval and the high peaked positive T-wave in Lead III persisted (Fig. 15).

Such a tracing may be difficult to classify in its proper type, unless it is kept in mind that in the early stages, particularly, the classification must be made on the basis of whether Lead I or Lead III presents alterations in the R-T interval similar to those in Lead II. Furthermore, it is important to remember that early in the process of infarction the T-waves may become more positive rather than inverted. On

this basis it is probable that this tracing should be classified as one of type T_3. Change in the level of the R-T interval and the inversion of the T-wave in Lead I may have come from one factor or from a combination of three factors. Depression of the level of the R-T interval is to be expected with infarction in the posterior surface of the left ventricle. The inverted T-wave may have been a relic of preponderant left ventricular strain due to hypertension, of the effect of chronic infarction in the apex and the anterior portion of the left ventricle, or of both these factors. Had further electrocardiograms been made, it would have been possible, probably, to make a more accurate analysis of the changes in the R-T interval in relation to infarction. However, it can be said that the major changes in the R-T segments in Leads II and III

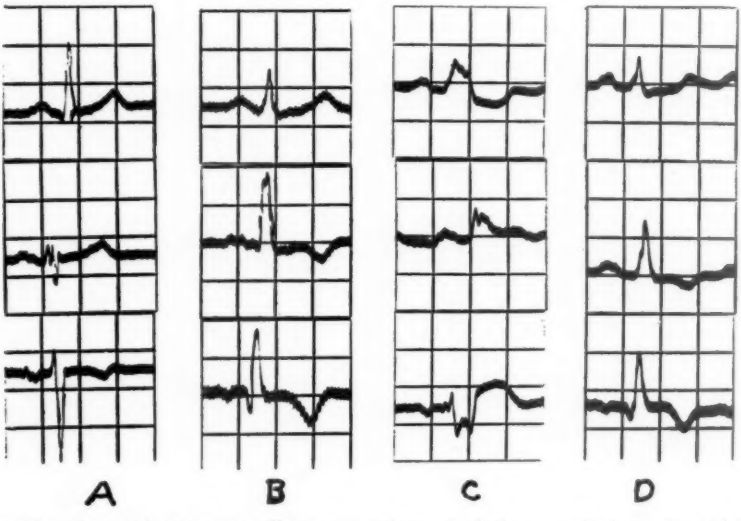


Fig. 16.—Case 10. Electrocardiograms taken *A*, before occlusion; *B*, thirty-six hours after acute infarction of the posterior portion of the left ventricle. The R-T interval in Leads II and III has a rounded contour. There is an exaggerated inverted T-wave in Lead III. *C*, incomplete bundle-branch block recorded on the day following the second infarction in the anterior portion of the left ventricle. *D*, tracing made five days after acute infarction. The R-T interval is elevated in Lead III and depressed in Lead I.

coincided with the more recent infarction in the posterior portion of the left ventricle.

CASE 10.—A man, 58 years old, came to the clinic because of precordial and substernal pain. He had been in extreme ill-health with hyperthyroidism for seven years, until thyroidectomy had been performed five years before the admission for the pain in the chest. Psychosis of three months' duration had followed this operation. The patient had been subject to definite attacks of angina pectoris for three years, and in one of these attacks he had fallen on the street. An electrocardiogram taken the day of his admission was essentially normal. The day following admission he had a seizure of excruciating thoracic pain, with features typical of coronary occlusion. The pain lasted for about ten hours and was followed by elevation in temperature, fall in blood pressure, and leucocytosis. An electrocardiogram was

taken thirty-six hours after the onset of symptoms of occlusion. The alterations of the R-T interval in Leads II and III, and its depression in Lead I (Fig. 16), led to an ante-mortem diagnosis of coronary occlusion, with infarction in the posterior portion of the left ventricle, in the region supplied in the average heart by the right coronary artery. Four days after his first attack the patient had a prolonged attack of pain suggesting further infarction. Following this, the electrocardiogram gave evidence of incomplete right bundle-branch block. On the basis that the right bundle-branch usually receives its chief blood supply from the anterior descending branch of the left coronary artery, this electrocardiographic abnormality led us to suspect that occlusive changes were occurring in the anterior descending artery or its branches.

At necropsy a thrombus was found in the right coronary artery just before the posterior descending branch was given off. The major acute infarction was in the posterior portion of the left ventricle and septum, extending practically to the apex. Minor acute infarction was observed in the anterior and septal portions of the left ventricle about 1 cm. from the apex. In the right and left coronary arteries there was sclerosis graded 3.

CASE 11.—A man, 58 years old, gave a history of having had an acute respiratory infection six weeks before admission. This had been followed by a wheezing cough, with pain over the anterior and posterior part of the chest. Following this, marked dyspnea had been noted, and for four or five weeks before admission the patient had been unable to lie down because of the dyspnea. Swelling of the lower extremities had been present for four weeks. On admission, the patient presented the general picture of congestive cardiac failure. The blood pressure was 176 systolic and 108 diastolic. The response to treatment was fairly prompt, but the patient was admitted in a similar condition one month later. Failure was gradual during the following six days, and death occurred from congestive cardiac failure and renal insufficiency.

At necropsy sclerosis, graded 2+, was found in the right coronary artery and in the left coronary artery, sclerosis, graded 3 was found. There was a small, old infarct at the juncture of the anterior portion of the ventricle with the septum, 1 cm. from the apex. A second chronic infarction was seen 2 cm. from the anterior interventricular sulcus and 2 cm. from the base. This was a wedge-shaped area 1 cm. in diameter, with its apex toward the endocardium. At the obtuse margin, in a region supplied jointly by the circumflex and the terminal branch of the right coronary artery, was a small amount of scattered fibrous tissue.

The electrocardiogram taken three months before death and eighteen days after the first admission of the patient, showed inversion of the T-wave in Leads I and II, with slight depressoin of the R-T segment in both leads (Fig. 17). This tracing was classified as probably of type T_1, chiefly because the changes in the R-T segment in Lead II resembled the characteristics formed in Lead I, whereas the R-T level in Lead III was unaltered. (Compare Fig. 17 with Fig. 5.)

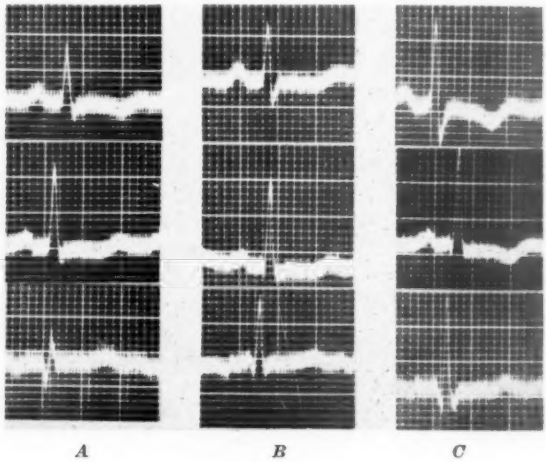
CASE 12.—A man, 54 years old, had had hypertension for ten years with a blood pressure ranging from 190 to 200 systolic. Four months before admission he had had an attack of severe dyspnea with a dull, aching pain in the precordium, which had lasted several hours and after which shortness of breath had been a prominent symptom. Eleven days before admission he had been seized with a sudden, sharp, knife-like pain in the precordium which had radiated down the lateral surface of the left arm as far as the elbow. There had been associated pallor, dyspnea, and

weakness. Relief had been obtained with morphine and nitroglycerine. Following the attack, his physician had found a low pulse pressure. The blood pressure on admission was 160 systolic and 140 diastolic. Death occurred from cerebral embolism the origin of which was an intracardiac thrombus at the apex of the left ventricle.

Sclerosis of the right and left coronary arteries, graded 2, was found. There was marked chronic and acute infarction of the anterior portion of the left ventricle, in its lower two-thirds, and of the anterior portion of the interventricular septum. There was marked thinning of the ventricle near the apex, with an organized thrombus underlying this area. This infarction was all in the region supplied by the anterior descending branch of the left coronary artery.

In the first electrocardiogram, made twelve days after the last severe seizure of precordial pain, the T-waves were diphasic in Leads I and II. On the following day, the T-wave was inverted in Lead I and

Fig. 17.



A B C

Fig. 18.

Fig. 17.—Case 11. Electrocardiogram of old infarction in the anterior portion of the left ventricle. The S-T interval is depressed in Leads I and II. There is a sloping S-T interval in Lead I and slight upward convexity in Lead II.

Fig. 18.—Case 12. *A*, electrocardiogram of old acute infarction in the anterior portion of the left ventricle, made twelve days after the last severe precordial pain and four months after the first attack of pain. The S-T interval in Lead I is rounded. The S-T interval in Leads I and II is slightly depressed. *B*, six days later; there are diphasic T-waves in Leads I and II. *C*, record made eight days after the first tracing. There is a downward sloping, slightly rounded S-T interval in Lead I.

diphasic in Lead II. In both leads, the R-T segment arose below the iso-electric line and in Lead I there was a slight upward convexity of the R-T segment. Six days later, the T-waves were inverted in Leads I and II and the R-T segment was typical of myocardial infarction. Death occurred eleven days after the last tracing was made (Fig. 18).

COMMENT

In the tabulation the cases have been divided into the types described. Study of these data shows that in twenty-one cases in which the electrocardiograms were definitely, less typical, or probably of

type T_1, the infarction occurred in the anterior and apical portion of the left ventricle, in the region supplied by the left coronary artery in the average heart. In six cases in which the electrocardiograms were of type T_3 infarction was found in the posterior portion of the left ventricle, the region supplied by the right coronary artery in the average heart. In four cases in which the electrocardiograms were of type T_3 and in one in which it was of type T_1, infarcts were found in both the anterior and posterior portions of the left ventricle.

In Case 3 the type of electrocardiogram which had been classified as type T_3 shifted to type T_1. It could be definitely established, in this case, that the old infarction was in the posterior portion of the left ventricle, in the region supplied by the right coronary artery and that the recent one was in the anterior surface of the left ventricle, in the region supplied by the left coronary artery.

In Cases 5 and 6 the type shifted from T_1 to T_3, with infarction in the anterior and posterior portions of the left ventricle. The older infarction in Case 5 occurred in the anterior portion and apex of the left ventricle. The probability is suggested that a similar condition existed in Case 6. Electrocardiograms showing curves of type T_1 or T_3 only, in patients with infarction in both the anterior and posterior portions of the left ventricle, probably indicate, according to the type present, the region in which infarction was more recent or more progressive. At any rate, successive electrocardiograms showing a definite shift from one type to another must lead to the strong suspicion that infarction has occurred in both the anterior and posterior portions of the left ventricle; and further, the latest type of change which occurs in the R-T interval usually will indicate the portion of the left ventricle in which the more recent or more extensive infarction has occurred.

In one case in a single electrocardiogram a curve was found that was classified as of a "less typical" type T_3 but the infarction was found to be in the anterior portion of the left ventricle. Cases such as this require further electrocardiograms before a definite opinion as to the type may be ventured. In the remaining cases the electrocardiograms could not be grouped according to types, and their correlation with the region of infarction in the left ventricle is not possible at present.

In these patients the most frequent site of infarction was in the region supplied by the anterior descending branch of the left coronary artery. The left coronary artery alone was responsible for infarction in twenty-five cases and the right coronary artery in eleven. However, including those cases in which infarction occurred in both the anterior and posterior portions of the left ventricle, we found the left coronary artery at fault in thirty-six cases and the right in twenty-two. These figures emphasize the fact that infarction in the portion of the left ventricle supplied by the right coronary artery is much more common than ordinarily is supposed.

This study indicates that an electrocardiogram of type T_1 is associated with infarction of the anterior portion of the left ventricle in the region supplied by the average left coronary artery. An electrocardiogram of type T_3 was found to be associated with infarction in the posterior portion of the left ventricle, in the region usually supplied by the right coronary artery. Parkinson and Bedford concluded that "all available evidence points to the fact that it is occlusion of the left coronary artery or its branches which produces characteristic T-waves of infarction." They recognized that infarction of the posterior surface of the left ventricle occurred when the right coronary artery was occluded, but they did not associate with its occlusion any changes in the T-wave characteristic of infarction. So far as we know, the present study is the first in which attention has been called to the fact that occlusion of the right coronary artery, producing infarction in the posterior portion of the left ventricle, causes characteristic changes in the R-T interval. Furthermore, so far as we know, this is the first study in which it is pointed out that changes in the R-T interval in infarction of the regions of the left ventricle that are supplied, in the average heart, by the right and left coronary arteries, respectively, are distinctly different and characteristic.

Our experience agrees with that of Parkinson and Bedford in that we found that gross infarction of the right ventricle was extremely rare. We have discussed elsewhere some probable anatomical explanations for this. Infarction of the right ventricle was found in only four cases of twenty-two in which occlusion of the right coronary artery or its branches was the source of injury. The infarction of the right ventricle in each case was minimal in amount and was closely adjacent to the injured posterior interventricular septum. In Case 12, in which the right coronary orifice was plugged by a thrombus, all of the right ventricle except a small area adjacent to the septum escaped infarction; this is not easily explained.

The electrocardiographic changes observed by Smith, in dogs, do not parallel the phenomena found by us in the human being following infarction. This is probably accounted for if one examines the difference between the distribution of the coronary arteries to the left ventricle of the dog[2, 8] and of man. In the dog the circumflex branch of the left coronary artery is much more important than in the average heart of human beings and supplies the posterior portion of the left ventricle and the interventricular septum. This region is supplied by the right coronary artery in the human heart, and infarction of this area in the human being was found to produce an electrocardiogram of type T_3. Smith did not discover significant changes in the T-wave on ligation of the right coronary artery in dogs, probably because the posterior surface of the left ventricle escaped infarction due to the fact that the right coronary artery did not supply this region.

In the study[1] of the effect of strain exerted predominantly on one ventricle, the conclusion was reached that strain predominantly of the left ventricle tended to cause inversion of the T-waves in Lead I or Leads I and II, whereas strain predominantly on the right side of the heart tended to cause inversion of the T-waves in the combined Leads II and III. Thus, as far as effect on the T-waves is concerned, infarction of the anterior portion of the left ventricle acts in the same general direction as strain predominantly of the left ventricle and infarction in the posterior portion of the left ventricle in the same direction as strain predominantly of the right ventricle. In the cases considered here there were nineteen of definite hypertension, in which electrocardiograms were of the type T_1 in fifteen. Inasmuch as hypertension produces inversion of the T-wave in the same leads as those in which inversion of the T-wave is observed in infarction of the anterior portion of the left ventricle, it cannot be denied that hypertension may have contributed in some measure to the T-waves observed in these cases. Hypertension does not determine the type of changes in the T-wave when infarction occurs in the posterior surface of the left ventricle. This was shown by the fact that in two cases of hypertension in which infarction in the posterior portion of the left ventricle was found, the changes in the R-T interval were of T_3 type. In a third case in which the electrocardiogram was of T_3 type, there was infarction in both anterior and posterior regions of the left ventricle. In one case there was an R-T interval of a less typical type T_3 which could not be explained on the basis either of hypertension or of infarction in the anterior portion of the left ventricle.

In seven cases there probably had been preexistent hypertension. In three of these cases there were changes in the R-T interval of type T_1, and in each case infarction was present in the anterior portion of the left ventricle. In four cases there were changes in the R-T segment of type T_3 and in each of these, infarction was found in the posterior part of the left ventricle.

In one case of aortic stenosis there was a change in the R-T interval of type T_1, and infarction of the anterior portion of the left ventricle was present. On the other hand, in a case of syphilitic aortitis and aortic regurgitation, presenting change in the R-T segment of type T_3 infarction in the posterior portion of the left ventricle was found.

Thus it appears that strain predominantly on one ventricle does not determine changes in the T-wave when this strain is competing with infarction. Furthermore, infarction, if it occurs in a region in which its effect on the T-wave is opposite to that of strain predominantly on one ventricle, the infarction will determine the form and direction of the changes in the R-T segment.

THEORETICAL CONSIDERATION

Elsewhere we have discussed the possible meaning of the observation that different portions of the left ventricle give rise to electrical effects acting in different directions on the T-wave. We pointed out that these results suggested that so far as effects on the T-wave were concerned, the left ventricle might be conceived of as being divided by a plane corresponding roughly with the line of division between the regions of the ventricle supplied by the right and the left coronary arteries in the average heart; and further, judging from their similar effects on the T-wave, the evidence at hand suggested that the posterior portion of the left ventricle acts on the T-wave in the same general direction as does the right ventricle. If this observation is correct, we suggest that it is not necessary to assume that the relatively small mass of muscle of the right ventricle alone produces electrical effects balancing those of the larger left ventricle.

It is probably more than a coincidence that this plane of division in the left ventricle follows the average plane of separation between the blood supply derived, respectively, from the right and from the left coronary arteries. However, it seems likely that it is the site of the area of infarction in the left ventricle rather than any particular blood supply that determines the changes in the R-T interval.

This leads to a consideration of the effect of the base and apex on the formation of the T-wave. Our results indicated that infarction confined to the apex produced changes of type T_1. When infarction of the anterior surface of the left ventricle and anterior septum was combined with infarction of the apex, the same type of change resulted. Infarction of the apex, together with infarction of the posterior region of the left ventricle produced a change of type T_3. In cases 16 and 27 there was infarction in the middle part of the ventricle with changes of type T_1, although in neither case could the electrocardiographic changes be said to be entirely typical of infarction. The area of the heart which produces electrical effects differing from those produced by the apex includes the right half of the basal two-thirds of the posterior surface of the left ventricle, but when the apex is involved in infarction, along with the latter area, the direction of the changes in the R-T interval is not determined by the apex. On the basis of their effects on the T-wave, it seems reasonable to assume from a study of these cases that the left ventricle may be divided into an anterior two-thirds including the apex, and a posterior one-third; this seems more reasonable than to consider the apex and base as exerting differential effects.

The anatomical architecture of the ventricular muscle as described by Mall, particularly the arrangement of the layers in the posterior surface of the left ventricle (Fig. 19) and their relation to the blood

supply, needs further study. Such study may help explain why the anterior and posterior portions of the left ventricle produce electrical effects acting in different directions.

It is impossible to state with certainty the mechanism of production of the normal T-wave in the electrocardiogram. It seems fairly certain that the T-wave is associated with the termination of the refractory period in the muscle fibers of the two ventricles. Katz and Weinman have concluded that the normal T-wave is due to the asynchronous cessation of electrical activity in the fractionate components of the ventricular muscle. The work of Wilson and Herrmann, as interpreted by Lewis, indicated that the T-wave is the resultant of electrical forces

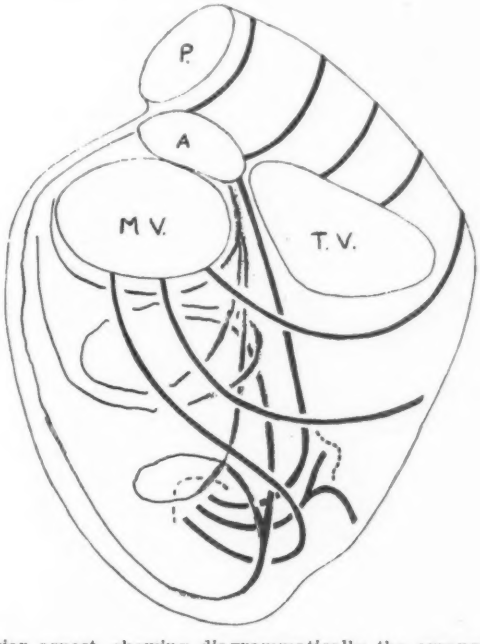


Fig. 19.—Posterior aspect, showing diagrammatically the arrangement of the chief muscle groups in the human heart. The sinospiral muscle group is in black and the bulbospiral in gray. The sinospiral muscle group, besides being distributed to the right ventricle, makes up a part of the basal three-fifths of the posterior portion of the left ventricle and of the interventricular septum in the region supplied by the average right coronary artery. *P*, pulmonary artery; *A*, aorta; *M.V.*, mitral ring; *T.V.*, tricuspid ring.

in the two ventricles and in that sense is a bicardiogram; and Lewis further interprets their investigations to mean that the upright T-wave in Lead I is predominantly a right ventricular effect, and the upright T-wave in Leads II and III is predominantly a left ventricular effect. The changes in the R-T interval observed in these cases are best explained when considered in the light of the conclusions of both of these investigations.

The various alterations of the R-T segment in myocardial infarction have as their common feature a deviation from the iso-electric level.

Careful study of these alterations shows that opposite effects often are observed in the early and in the later stages of infarction. In the first few days after infarction the R-T wave usually rises above the iso-electric level; it may have an upward convexity, or it may rise to a summit in a T-wave at the end of the plateau. In the course of a few days, or at most in two or three weeks' time, the level of the R-T segment returns to or below the zero level, and the T-wave becomes inverted. This strongly suggests that the initial alteration of electrical effects in the infarcted area differs from the later alterations. Finally, the R-T segment usually returns to normal, and the inversion of the T-wave disappears; this change requires months and sometimes one to two years for its completion.

It is impossible to discuss the mechanism involved in the effect of infarction on the R-T interval without a knowledge of the effect of infarction on conduction time and duration of electrical activity of the muscle fibers in the area involved. It is likely that these effects will be found to be, in the first few days after infarction, different and probably opposite from those occurring subsequently. It seems reasonable to assume that the effects on the R-T interval in infarction are the result of alterations in the electrical activity of the area of the infarct and that the resultant of electrical forces which produce the normal R-T interval are disturbed. Furthermore, it is reasonable to assume that when there is infarction of one portion of the ventricle, the electrical activity in the relatively uninjured portion and in the opposite ventricle occurs in the same direction as before. The solution of the problem of alterations in electrical effects in infarcted cardiac muscle will contribute greatly to a knowledge of the exact mechanism in the production of the inverted T-waves and, by inference, to better understanding of the factors responsible for the upright T-wave.

SUMMARY AND CONCLUSIONS

1. The importance of a study of infarction in relation to the distribution in the left ventricle of the right and left coronary arteries has been pointed out.

2. The branches of the arteries which supply the left ventricle, whether they originate from the right or the left coronary artery, are similar in architecture.

3. It has been shown that in the distribution of the right coronary artery in the right ventricle, branches leave the main artery in the same general plane as that of the branch from which they arise, whereas, in the left ventricle, they leave the coronary artery at right angles and penetrate directly through the myocardium.

4. Myocardial infarction of the right ventricle is rare.

5. Infarction which follows occlusion of the right coronary artery or its branches almost always is found in the posterior portion of the

left ventricle and septum and at times in the apex. The area that becomes infarcted depends on the distribution of the right coronary artery in the left ventricle.

6. Occlusion of the left coronary artery usually involves its anterior descending branch, although occasionally the circumflex branch is the site of occlusion. In occlusion of the anterior descending branch, infarction at the apex and in variable portions of the anterior portion of the left ventricle and septum are the rule.

7. Infarction of the left ventricle produces characteristic changes in the R-T segment of the electrocardiogram. The essential change is considered to be the fact that the R-T interval fails to establish an isoelectric level. From a study of the electrocardiogram, the changes usually can be classified as of types T_1 and T_2 as suggested by Parkinson and Bedford.

8. Infarction limited to the anterior portion of the left ventricle, either alone or combined with infarction of the apex, or infarction of the apex alone, produces modifications of the R-T segment of type T_1, whereas infarction of the posterior portion of the left ventricle, with or without infarction of the apex, produces modifications of the R-T interval of type T_3.

9. In cases in which infarction occurred in both areas at successive intervals of time, there was a corresponding shift in the changes in the R-T segment, and the last change observed corresponded with the last portion undergoing infarction.

10. On the basis of its effects on the R-T wave of the electrocardiogram, the left ventricle may be conceived of as being divided by a plane on either side of which the electrical forces which produce the R-T interval act in different directions. Apparently this plane of division in the left ventricle corresponds roughly to the usual line of division between the distribution of the right and left coronary arteries. Results of a previous investigation indicated that right ventricular strain was associated at times with inversion of the T-wave in Leads II and III. Inasmuch as these are the two leads in which occurred the chief changes in the R-T interval and, later, inversions of the T-wave in cases of infarction of the posterior portion of the left ventricle, it is suggesetd that in the posterior region of the left ventricle the electrical effects on the T-wave act in the same direction as those in the right ventricle.

11. It is suggested that the infarcted portion acts as a unit with reference to the remaining relatively normal fibers and that in the infarcted region there is some disturbance of the normal activation of the muscle fibers or of the duration of their electrical activity. Physiologic experiment determining whether fibers of the infarcted area

emerge from the refractory stage late or early as compared to the relatively normal fibers may throw some light on the mechanism of the alteration of the R-T wave.

12. So far as this study goes, the results indicate that typical alterations of the R-T interval in infarction of the left ventricle are characteristic in type and enable one to localize the region involved. The identification of the region involved usually will indicate which coronary artery is the seat of trouble.

TABULATION

CLASSIFICATION OF ELECTROCARDIOGRAMS ACCORDING TO TYPES

	SITE OF THE INFARCTION IN RELATION TO THE CORONARY ARTERIES			
	CASES	LEFT CORONARY ARTERY	RIGHT CORONARY ARTERY	BOTH
Typical types				
T_1 or T_3				
T_1	5	4		1
T_3	5		3	2
T_1 to T_3	1			1
T_3 to T_1	1			1
Less typical types				
T_1 or T_3				
T_1	10	10		
T_3	5	1	2	2
T_1 to T_3	1			1
T_3 to T_1				
Probable types				
T_1 or T_3				
T_1	7	7		
T_3	1		1	
T_1 to T_3				
T_3 to T_1				
Indeterminate types				
T_1 or T_3				
T negative in Leads I, or in I and II	2	1*	1†	
T negative in Leads III or in II and III	1		1†	
Inverted T in Leads I, II, III	1		1	
Bundle-branch block				
Complete or incomplete right	6	2	2	2
Complete or incomplete left	1			1

*T waves diphasic in Leads I and II and iso-electric in Lead III.
†Tracing lost.

REFERENCES

1. Barnes, A. R., and Whitten, M. B.: Studies of T-Wave Negativity in Predominant Ventricular Strain, AM. HEART J. 5: 14, 1929.
2. Baumgarten, W.: Infarction in the Heart, J. Physiol. 2: 243, 1899.
3. Gross, Louis: The Blood Supply to the Heart in Its Anatomical and Clinical Aspects, New York, P. B. Hoeber, 1921.
4 Herrick, J. B.: Thrombosis of the Coronary Arteries, J. A. M. A. 72: 387, 1919.

5. Katz, L. N., and Weinman, S. F.: The Relation of the T-Wave to the Asynchronism Between the Ends of the Right and Left Ventricular Ejection, Am. J. Physiol. **81**: 360, 1927.
6. Lewis, Thomas: The Mechanism and the Graphic Registration of the Heart Beat, London, 1925, ed. 3, p. 122, Show and Sons, Ltd.
7. Mall, F. P.: On the Muscular Architecture of the Ventricles of the Human Heart, Am. J. Anat. **11**: 211, 1911.
8. Miller, J. L., and Mathews, L. A.: Effect on the Heart of Experimental Obstruction of the Left Coronary Artery, Arch. Int. Med. **3**: 476, 1909.
9. Pardee, H. E. B.: An Electrocardiographic Sign of Coronary Artery Obstruction, Arch. Int. Med. **26**: 244, 1920.
10. Pardee, H. E. B.: Heart Disease and Abnormal Electrocardiograms, With Special Reference to the Coronary T-Wave, Am. J. Med. Sc. **169**: 270, 1925.
11. Pardee, H. E. B.: Clinical Aspects of the Electrocardiogram; a Manual for Physicians and Students, New York, 1928, P. B. Hoeber.
12. Parkinson, John, and Bedford, D. E.: Successive Changes in the Electrocardiogram After Cardiac Infarction (Coronary Thrombosis), Heart **14**: 195, 1928.
13. Smith, F. M.: The Ligation of Coronary Arteries With Electrocardiographic Study, Arch. Int. Med. **22**: 8, 1918.
14. Spalteholz, Werner: Die Arterien der Herzwand; Anatomische Untersuchungen an Menschen- und Tierherzen, nebst Erörterung der Voraussetzungen für die Herstellung eines Kollateralkreislaufes, Leipzig, 1924, S. Hirzel.
15. Whitten, M. B.: A Review of the Technical Methods of Demonstrating the Circulation of the Heart, Arch. Int. Med. **42**: 846, 1928.
16. Whitten, M. B.: The Relation of the Distribution and Structure of the Coronary Arteries to Myocardial Infarction, Arch. Int. Med. (In press.)
17. Wilson, F. N., and Herrmann, G. R.: An Experimental Study of Incomplete Bundle-Branch Block, and of the Refractory Period of the Heart of the Dog, Heart **8**: 229, 1921.

THE AGE AND SEX INCIDENCE OF ARTERIAL HYPERTENSION*

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IT HAS often been stated that essential hypertension† is found most frequently among middle-aged and pre-elderly individuals. In only a few instances, however, have the statements been accompanied by statistics. Similarly, although the condition has been said to be more common among men than among women, the basis for establishing this as a fact has not been presented.

There are few data available that concern directly either the age or the sex incidence of hypertension. However, a number of contributions appear in the literature, which contain reference to the ages of patients who were presented as illustrations of various aspects of hypertension or sphygmomanometry. Tables I-A—I-E compare the results of some of these investigations calculated and arranged according to the percentage of patients in different age periods.

These reports have been separated into four groups as follows: A, hypertension as found in different periods of life; B, age of patients with hypertension at time of death; C, life insurance statistics; D, E, hospital reports. This classification is necessary for a discussion of the age incidence of hypertension because each group possesses characteristics which make it difficult to compare one group with another.

HYPERTENSION AS FOUND IN DIFFERENT PERIODS OF LIFE

Early Childhood.—Amberg[1] reported 25 instances of increased blood pressure found in children from six to sixteen years of age. Nine of these cases were in all probability of the essential hypertension type, and four of the nine had no detectable renal involvement. These 9 cases are not included in Table I-A because of the rarity of hypertension in early childhood. There are other instances given in the literature of hypertension in children, but the increase in blood pressure was probably secondary to a coexisting nephritis.

Hypertension in Youth.—There are three significant reports concerning blood pressure examinations of persons from sixteen to forty years of age. The investigators have usually considered 140 mm. Hg to be the dividing line between a normal and an abnormally high systolic blood pressure. Alvarez[2] in a report of the blood pressure

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†The term "essential hypertension" is used to define persistent high blood pressure in the larger circulation due to other causes than primary genitourinary disease.

readings of about 260 drafted men showed that 141 had a systolic pressure above 140 mm. Hg. If a calculation is made in terms of the percentage of frequency with which the individuals fall into various age groups (Table I-A), it is found that there is a close approximation

TABLE I-A

THE RELATIVE FREQUENCY WITH WHICH THE DIAGNOSIS OF HYPERTENSION IS MADE AT VARIOUS PERIODS OF LIFE*

AGE	Alvarez (2)		Alvarez, Wulzen, Mahoney (3)				Diehl, Sutherland (4)		Wildt (9)		Bowes (10)		Richter (11)		AGE
	Total cases examined 263 Men	Cases of hypertension 141 Men	Total cases examined 6,000 Men	Cases of hypertension 1,245 Men	Total cases examined 8,934 Women	Cases of hypertension 246 Women	Total cases examined 5,122 Men	Cases of hypertension 586 Men	Total cases examined 248 Both sexes	Cases of hypertension 101 Both sexes	Total cases examined 50 Men	Total cases examined 100 Women	Total cases examined 165 Both sexes	Cases of hypertension 83 Both sexes	
90									1.6	1.	8.0	3.0			90
80									5.6	8.9		7.0	9.1	10.8	80
70									16.1	14.9	22.0	16.0	14.5	15.7	70
60									23.	20.8	28.0	24.0	31.5	31.3	60
50									27.4	25.8	20.0	29.0	21.2	22.9	50
40	28.1	28.3	1.2	1.	2.5	9.3	0.3	0.2	15.7	18.8	22.0	21.0	17.6	15.7	40
30	36.1	36.2	2.2	1.5	4.5	7.7	0.9	0.7	10.5	9.9			6.1	3.6	30
20	1.9	1.4	8.9	7.4	10.4	6.9	6.5	5.1							20
10	19.8	21.2	39.3	39.1	30.4	25.2	33.6	35.7							10
	14.1	12.8	48.6	51.	52.	50.8	58.8	58.2							

*Calculated and arranged in terms of percentage of total diagnoses occurring in each age group.

between the age distribution of the 141 cases of hypertension and the total 263 cases whose systolic blood pressures were recorded. Alvarez, Wulzen, and Mahoney[3] have reported the blood pressure readings of 14,934 college freshmen, both men and women. The age distribution of

the 1245 men with hypertension was very similar to that of the entire 6,000 men examined. Of the 8,934 women who were examined, 246 had a systolic pressure of 140 mm. Hg or over. The age distribution of the women with high blood pressure ran parallel with that of the entire group except between the ages of thirty-six and forty years where there was an actual as well as a relative increase in the frequency of individuals with hypertension. Diehl, and Sutherland[4] have presented a similar investigation on the blood pressures of 5,122 college men. Here again the age distribution of the 586 men with increased blood pressure was similar to that of the entire group.

These investigators have found hypertension to be surprisingly common among young men. Considering all the men examined, regardless of age, Alvarez found hypertension in 53.6 per cent of drafted men; Alvarez, Wulzen and Mahoney found it in 20.7 per cent of male college freshmen; while Diehl and Sutherland found it in 11.5 per cent of men in the first year of college. This frequency becomes more striking when hospital statistics are considered which include persons from youth to senility. The latter type of investigations showed hypertention to exist in 9.6 per cent (Obuch Institut für Gewerbekrankheiten, Moskau[5]) and 9.7 per cent (Universitäts Klinik, Kiel[6]) of the male patients examined.

Alvarez, Wulzen and Mahoney found hypertension in 2.8 per cent of the young women they examined. The hospital statistics mentioned above demonstrated hypertension to be present in 7.9 per cent[5] and 25.9 per cent[6] of the total number of women examined.

The three investigations on hypertension in youth possess one common characteristic, namely, that the examinations were made on normal individuals in whom there was no reason to suspect ill health. Moog and Voit[7] have reported 16 instances of hypertension in patients between sixteen and twenty-eight years of age, and Magniel[8] has presented 3 similar cases. These patients differed from those discussed above in that they suffered from ill health and their hypertension required treatment.

Hypertension in Old Age.—Wildt[9] reported the blood pressure readings of 248 patients between sixty and ninety-six years of age, 101 of whom had systolic blood pressures of over 150 mm. Hg. Forty-seven per cent of the cases of hypertension and 50 per cent of the total patients examined were between seventy and seventy-nine years of age. The age distribution of the cases with hypertension was similar to that of the entire group. Bowes[10] determined the blood pressure of 100 women and 50 men above sixty-four years of age, the majority of whom had hypertension. The distribution of the men, according to five year age periods, showed the greatest incidence between seventy-five and seventy-nine years of age. The same calculation for the women showed the period of maximum incidence five years earlier

than in the men. Richter[11] observed the blood pressure in 165 elderly individuals between the ages of sixty and eighty-nine years, 83 of whom had a systolic pressure of 150 mm. Hg or more. The greatest

TABLE I-B

THE RELATIVE AGE DISTRIBUTION OF PATIENTS WITH HYPERTENSION, AT THE TIME OF DEATH*

AGE	Shaw (12)	Bell and Hartzell (13)				Bell, Clawson (14)	AGE
	Cases of hypertension 47 Both sexes	Total cases examined 1,529 Men	Cases of hypertension 120 Men	Total cases examined 542 Women	Cases of hypertension 23 Women	Cases of hypertension 417 Both sexes	
90						2.4	90
80	8.	5.8	9.2	5.2	13.	11.5	80
70	16.	16.1	27.5	12.1	13.	27.6	70
60	20.	23.9	40.8	17.9	34.8	32.9	60
50	32.	20.1	13.3	18.3	26.	16.3	50
40	12.	20.5	8.3	19.6	13.	6.7	40
30	6.	13.5	0.8	26.9		1.9	30
20						0.7	20
10							10

*Calculated and arranged in terms of percentage of total diagnoses occurring in each age group.

age incidence occurred in the seventy-five to seventy-nine year group. The curve for the age distribution of hypertension among the 83 individuals closely approximates that for the age distribution of the entire group of 165 persons.

AGE INCIDENCE OF HYPERTENSION AT TIME OF DEATH

Hypertension may be an indirect cause of death. Presumably the high blood pressure in the cases to be discussed (Table I-B) had existed for some time before death; nevertheless, the patients show a wide distribution of ages. Shaw[12] studied the clinical histories and post-mortem findings of 50 cases in which the systolic blood pressures were above 150 mm. Hg. The heaviest incidence was found in the forty to forty-nine year age group. No control figures were given. Bell and Hartzell[13] have recorded the results of 2071 necropsies including 120 men and 23 women who had had hypertension. These patients with hypertension varied from twenty-one to ninety years of age. The greatest incidence of the cases was for patients between fifty-one and sixty years of age. Bell and Clawson[14] have reported 420* autopsies on patients with hypertension who ranged from thirteen to ninety years of age. In 184 instances the diagnosis of hypertension was made on the basis of the post-mortem weight of the heart. Sixty per cent of the patients with hypertension were between the ages of fifty-one and seventy years of age. The decade from fifty-one to sixty years showed the greatest number of cases of hypertension.

LIFE INSURANCE STATISTICS

Large life insurance companies require a medical examination of each applicant. From time to time there has been presented information based on the results of these examinations. These reports do not include the results of all the examinations, because the data for those applicants accepted for life insurance have usually been separated from those for individuals who were rejected because of physical ailments. As a result of this, life insurance statistics on hypertension possess certain peculiarities. Were it possible to combine the data obtained from these two sources, the result would still fall short of representing a cross-section of the physical condition of the community, because those who apply for life insurance represent for the most part individuals who believe themselves to be in perfect health. From this comparatively healthy group of applicants the medical examiners weed out those whose blood pressures are abnormally high as well as those who show some of the complications of hypertension and whose prognosis, therefore, is unfavorable. Furthermore, old age is in itself a handicap to acceptance for life insurance, and as a result there are few figures for persons above sixty-five years of age.

The accepted risks, therefore, represent a selected group of persons with hypertension under sixty-five years of age. These selected individuals usually have only moderately elevated blood pressures and no complications. The rejected risks include only a portion of the remaining cases of hypertension in the community, for elderly individ-

*The ages of 417 patients were recorded.

uals and those who know themselves to be suffering from hypertension or other ailments rarely present themselves for life insurance. The importance of this division of cases is illustrated by the figures of Van Wagenan,[15] which show 5.7 per cent of the accepted individuals and

TABLE I-C

THE RELATIVE FREQUENCY OF HYPERTENSION AS SHOWN BY LIFE INSURANCE STATISTICS*

AGE	Fisher (16)		Fisher (19)	Symonds (17)				Frost (20)		Dublin, Fisk, Kopf. (21)		Rogers, Hunter (22)	AGE
	3156 Accepted risks with hypertension	1274 Risks rejected because of hypertension	4165 Risks rejected because of hypertension	Total accepted risks 150,419 Men	Cases of hypertension 8,579 Men	Total accepted risks 11,937 Women	Cases of hypertension 422 Women	Total cases examined 146,992 Both sexes	Cases of hypertension 2,568 Both sexes	Total accepted risks 16,662 Men	Cases of hypertension 1,199 Men	4,214 Accepted risks with hypertension	
90													90
80													80
70									7.				70
60	8.6	16.7		1.3	6.7	0.3	1.7	1.	11.				60
	8.9	14.7	35.9	2.4	10.3	1.4	12.1	2.	15.	6.6	21.	28.2	
50	18.4	22.		4.9	14.5	3.2	16.1	7.	17.	18.2	25.5		50
	33.2	26.	28.7	8.6	17.8	7.3	27.3	10.	13.			33.4	
40	31.1	20.4		12.2	15.4	9.8	19.9	15.	10.	34.8	26.5		40
			17.5	15.4	12.4	13.2	11.1	18.	8.				
30				17.9	9.7	17.2	6.4	18.	7.	35.3	23.5	38.4	30
			17.8	18.4	7.7	22.6	3.3	16.	7.				
20				13.9	4.6	19.8	1.7	9.	3.	5.2	3.4		20
				4.8	0.8	5.3	0.5						
10													10

*Calculated and arranged in terms of percentage of total diagnoses occurring in each age group.

22.5 per cent of the declined persons to be between fifty-six and seventy years of age. The "declined risks" were refused insurance because of various ailments. Fisher's figures[16] show the ages of those individuals who were refused life insurance solely because of ele-

vated blood pressure. In his series 31.4 per cent of the rejected candidates were between fifty-four and sixty years of age, while only 17.5 per cent of the accepted individuals fell into this same age group.

Although there is evidence to show that the age at which hypertension is most likely to occur is not the same in both men and women, the life insurance reports do not always indicate the sex of the applicants. Judging from the figures of Symonds[17] over 90 per cent of the applicants are men.

Many life insurance companies instruct their medical examiners to consider that hypertension exists if there occurs a persistent systolic pressure of 15 to 20 mm. Hg above the average for persons of the same age and sex; other companies consider 139 mm. Hg to be the upper limit of normal systolic blood pressure regardless of the age or sex of the individual. These figures are perhaps a little lower than those considered by many internists to indicate hypertension. So far as it is known, there is no universally accepted dividing line between normal and high blood pressure. Osler[18] in his *Practice of Medicine* sets the dividing line at 160 mm. Hg, and this is a figure which is in common use, although in childhood and early youth lower blood pressure would be considered as abnormal. At the present time more attention is being paid to the diastolic pressure than formerly. A patient may be considered to be suffering from hypertension who has a diastolic pressure in the neighborhood of 100 mm. Hg, even though the systolic pressure is only moderately elevated.

The accepted individuals recorded by Fisher[16] show their greatest incidence to be between the ages of forty-five and forty-nine. On the contrary, the rejected persons had the peak of their age incidence between fifty-four and sixty years of age. A later report by the same author[19] concerning only rejected cases shows essentially the same age distribution as the previously rejected individuals. The figures for the men and the women were not separated in this report, and no control figures were given.

Symonds[17] analyzed the blood pressure readings of over 162,000 accepted risks and found 8,579 men and 422 women with systolic pressures over 140 mm. Hg. The significance of this figure as the dividing line between normal and abnormally high blood pressure is shown by the fact that of this group there were only 704 men and 38 women whose pressures were above 150 mm. Hg and only 372 men and 22 women with systolic readings above 155 mm. Hg. Symonds showed the greatest incidence of those individuals whose pressures were above 140 mm. Hg to occur between forty-five and forty-nine years of age in both men and women, with a relatively higher incidence among women in the five years preceding this age group.

Frost[20] has presented 2,568 cases of hypertension which were discovered through the medical examinations of 146,992 applicants for life

insurance. Many of the cases with known cardiovascular or renal disease were not included in the group with hypertension. The cases of hypertension occurred in both sexes, the individuals ranging from fifteen to seventy years of age. The graph presented by Frost from which the data in Table I-C were approximated shows a gradual rise in the incidence of hypertension, reaching a maximum in the fifty to fifty-four year age period and slowly falling off thereafter.

Dublin, Fisk and Kopf[21] have reported statistics on 16,662 male policy holders including 1,199 men with hypertension. These authors found hypertension in 5.5 per cent of the policy holders between thirty-five and forty-four years of age and in 23 per cent of the "accepted risks" who were more than fifty-five years old. There were, however, relatively few elderly policy holders, and as a result the greatest number of persons with hypertension were found to be between thirty-five and forty-four years of age.

Rogers and Hunter[22] noted that of 4,214 accepted cases of hypertension, the greatest incidence occurred in individuals between forty and forty-nine years of age. The men and women were considered together and no controls were presented.

HOSPITAL REPORTS

This group consists of reports from various hospitals in Europe and America and includes patients ranging from ten to eighty-nine years of age (Table I-D).

Weitz[23] reported 64 instances of hypertension discovered in the Medical and Nerve Clinic at Tubingen. The fifty-six to sixty year group contained the largest number of cases.

Gelman[5] has presented the blood pressures of 3,761 patients from the Obuch Institut für Gewerbekrankheiten, Moskau. These cases included 255 men and 89 women whose systolic blood pressure was above 140 mm. Hg. The greatest incidence of hypertension among the men occurred in those between forty and forty-nine years of age with only slightly fewer in the succeeding decade. These twenty years accounted for 60 per cent of the total number of men whose blood pressures were elevated. Over 75 per cent of the women with hypertension were between thirty and forty-nine years of age, and a majority of these individuals were between thirty and thirty-nine years old.

The ages and blood pressures of over 4,000 patients of the Universitäts Klinik at Kiel have been recorded by Saller.[6] These included 232 men and 453 women whose systolic pressures were greater than 143 mm. Hg. The maximum age incidence for hypertension in both men and women occurred between the ages of fifty-one and fifty-nine The distribution among the younger age groups was quite different in the two sexes; about 27 per cent of the male and 10 per cent of the female patients with hypertension being less than forty-two years of age.

Hypertension in this series of patients appeared at an earlier age among men than among women.

Eighty-one cases of "malignant hypertension" have been collected by Keith, Wagener and Kernohan[24] from the Mayo Clinic. In all save

TABLE I-D

THE RELATIVE FREQUENCY OF HYPERTENSION AS SHOWN BY HOSPITAL REPORTS*

AGE	Weitz (23)		Gelman (5)				Saller (6)				Keith et al (24)		AGE
	Total cases examined 359 Both sexes	Cases of hypertension 64 Both sexes	Total cases examined 2,641 Men	Cases of hypertension 255 Men	Total cases examined 1,120 Women	Cases of hypertension 89 Women	Total cases examined 2,385 Men	Cases of hypertension 232 Men	Total cases examined 1,743 Women	Cases of hypertension 453 Women	Cases of hypertension 48 Men	Cases of hypertension 33 Women	
90													90
80													80
70	11.4	21.8					3.9	13.3	5.2	14.9			70
	14.7	23.4	0.7	2.			8.	21.1	7.9	19.8	2.1	3.	
60	23.9	34.3									4.2	0.	60
	20.3	15.6	8.7	27.8	3.1	10.1	13.3	23.7	16.9	33.8	14.6	24.3	
50	29.5	4.7									27.1	18.2	50
			20.9	32.5	12.6	30.3	16.8	15.2	18.9	22.	18.7	21.2	
40											18.7	12.1	40
			31.2	19.6	34.2	47.2	24.4	14.2	23.1	6.2	6.2	9.1	
30											4.2	3.	30
			33.6	14.1	45.5	11.2	20.7	9.9	17.1	2.4	0.	3.	
20			4.7	3.9	4.5	1.1		2.6		0.7	2.1	6.1	20
							13.5		10.9		0.	0.	
10											2.1	0.	10

*Calculated and arranged in terms of percentage of diagnoses occurring in each age group.

one of these cases the systolic pressure was above 220 mm. Hg. In both sexes hypertension occurred with considerable frequency after thirty years of age, the maximum incidence being in the forty to forty-nine year group.

BOSTON CITY HOSPITAL RECORDS

The data about to be presented have been derived from the records of both the wards and the out-patient department of the Boston City Hospital. It is necessary to consider the statistics from each of these

TABLE I-E

THE AGE INCIDENCE OF HYPERTENSION, AS FOUND IN THE BOSTON CITY HOSPITAL*

AGE	Out-patient Department				Hospital Wards				AGE
	Controls 606 Men	Cases of hypertension 442 Men	Controls 607 Women	Cases of hypertension 1,170 Women	Controls 851 Men	Cases of hypertension 499 Men	Controls 447 Women	Cases of hypertension 574 Women	
							0.5	0.2	
90		0.3		0.1	0.1	0.6	0.5	0.2	90
		1.1		0.3	1.	1.8	1.	0.5	
80	1.5	3.6	0.2	1.5	1.3	3.	3.1	3.5	80
	4.	6.5	0.8	3.2	4.	6.8	3.4	7.9	
70	4.1	16.3	2.1	9.3	5.9	14.9	6.1	11.	70
	6.1	25.5	4.8	17.7	6.9	18.8	9.4	18.8	
60	7.9	10.6	5.4	16.5	10.6	15.4	8.3	13.6	60
	12.	16.9	8.7	17.9	10.9	12.8	7.6	18.3	
50	9.9	6.7	10.9	17.3	10.	8.4	7.4	8.5	50
	10.	5.4	10.7	8.1	8.9	7.6	6.9	6.3	
40	9.1	2.3	13.7	5.3	9.4	3.4	6.9	5.6	40
	7.1	1.8	9.5	1.8	8.8	2.6	9.6	2.8	
30	6.1	0.9	9.5	1.	9.2	1.8	9.	1.7	30
	7.9	0.9	9.2	0.	7.2	1.2	10.5	0.7	
20	8.2	0.9	7.9	0.3	3.6	0.6	6.9	0.	20
	5.9		6.4		2.4	0.2	2.9	0.5	
10									10

*Calculated and arranged in terms of the percentage of total diagnoses which occurred in each five-year age group.

sources separately, for they represent different clinical types of patients. The majority of those patients who entered the wards for treatment were seriously ill, and if they had hypertension, they were suffering in the majority of instances from one or another of the major

complications of this condition. The out-patient cases of hypertension, on the other hand, occurred in relatively healthy individuals and usually without complications.

From April, 1925, until December, 1928, inclusive, 1620 diagnoses of hypertension were made in the medical out-patient department. The age of eight of the patients was not recorded. A few of the individuals considered they were well and were examined to determine if ill health existed. The rest of the patients submitted themselves for examination because of symptoms which did not prevent them from walking to the hospital. Seldom were patients discovered to be so seriously ill as to make it desirable for them to enter a hospital ward.

The blood pressure of all patients was taken by the auscultatory method using the Riva-Rocci type of sphygmomanometer with a 12.5 cm. cuff. The diagnosis of hypertension was made by the various members of the staff. An analysis of the blood pressure readings of 1600 of the total number of cases showed that the systolic pressures were 160 mm. or over in 91.6 per cent, and in only 3.1 per cent were the systolic readings less than 150 mm. Hg. The diastolic pressures were less frequently elevated; 66.1 per cent of the cases had a diastolic pressure of 100 mm. Hg or more, and in 85.9 per cent it was 90 mm. Hg or more. These cases of hypertension may be said to have been of two classes: those in which the systolic pressure was only moderately elevated, but in which the diastolic reading was in the neighborhood of 100 mm. Hg; and second, those in which both the systolic and diastolic pressures were considerably elevated.

Of the total group of out-patient cases, 281 or 17.3 per cent exhibited evidence of impaired kidney and cardiac function or cerebral hemorrhage. In a number of patients special studies were made in order to determine if any complications existed. These tests included electrocardiographic tracings, nonprotein nitrogen determinations on the blood and various renal function tests.

During the three years 1925-1927, 1104 patients with hypertension entered the wards. The age of 31 patients was not determined. Seven hundred and twenty or 65.2 per cent had a disorder of the heart, kidney or brain. Thus, there was a much higher incidence of complications among the ward cases than among the out-patient cases with hypertension. The medical services contributed 90.3 per cent of the total cases and the neurological and surgical services contributed 4.4 per cent and 3.5 per cent respectively. The few remaining cases were reported from the gynecological, obstetrical, dermatological, pediatric and aural services.

The blood pressures of the ward patients with hypertension tended to be higher than the out-patient cases. The systolic blood pressures in 95.3 per cent of 300 consecutive ward cases were 160 mm. Hg or more, and only 2.7 per cent of these cases had a systolic pressure of less than

150 mm. Hg. The diastolic pressures also were elevated in a large percentage of the cases, in 82 per cent it was 100 mm. Hg or over. Fifty-five per cent of the ward cases had systolic pressures of 200 mm. Hg or over, while only 33 per cent of the out-patient cases had systolic pressures of the same magnitude.

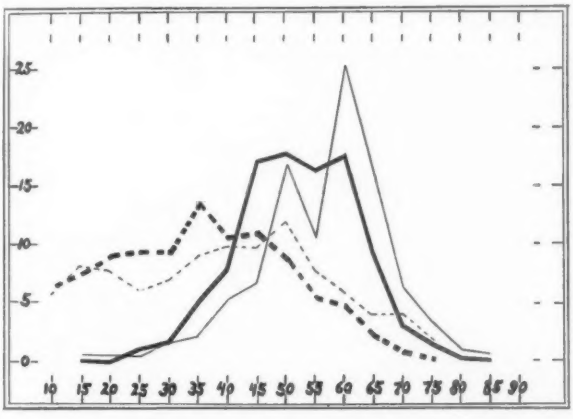

Fig. 1.—Graphic presentation of age incidence of out-patients with hypertension with that of the clientele of the Out-Patient Department of the Boston City Hospital. The abscissa represents the age period in years, the ordinate the percentage of the total number of cases. The male patients with hypertension are represented by the thin continuous line, the female patients by the thick continuous line. The control male cases are represented by the thin interrupted line, the control female cases by the thick interrupted line.

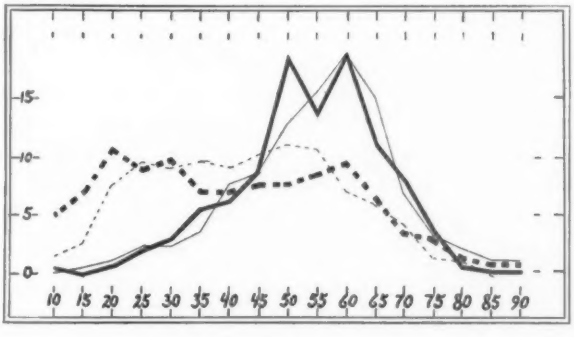

Fig. 2.—Graphic presentation of age incidence of ward patients with hypertension with that of the clientele of the medical wards of the Boston City Hospital. The abscissa represents the age period in years, the ordinate the percentage of the total number of cases. The male patients with hypertension are represented by the thin continuous line, the female patients by the the thick continuous line. The control male cases are represented by the thin interrupted line, the control female cases by the thick interrupted line.

Table I-E and Figs. 1 and 2 show the percentage frequency with which hypertension was found at various ages. The figures are arranged in terms of the percentage of cases which occurred in each five year age group. A few cases were found in individuals between twelve and twenty years of age, but hypertension did not occur with a frequency

above 10 per cent in the five-year groups below forty years of age. After the age of seventy the incidence of hypertension dropped quite sharply. Among women the condition occurred earlier in life than in the men. This was especially evident in the out-patient cases where the curve for the incidence among women showed a rise a full five years before there was a similar rise for the men. More than half the cases

TABLE II

INCIDENCE OF HYPERTENSION AT DIFFERENT AGES CONTRASTED WITH THAT FOR THE CLIENTELE, BOSTON CITY HOSPITAL

AGE	MEDICAL OUT-PATIENT DEPARTMENT				HOSPITAL WARDS			
	Hypertension 1612 Cases		Control 1213 Cases		Hypertension 1073 Cases		Control 1278 Cases	
	Men 442	Women 1170	Men 606	Women 607	Men 499	Women 574	Men 831	Women 447
10-14			36	39	1	3	20	13
15-19	4	4	50	48	3	0	30	31
20-24	4	0	48	56	6	4	60	47
25-29	4	12	37	58	9	10	76	40
30-34	8	20	43	58	13	16	73	43
35-39	10	62	55	83	17	32	78	31
40-44	24	95	61	65	38	36	74	31
45-49	30	201	60	66	42	49	83	33
50-54	75	209	73	53	64	105	90	34
55-59	47	193	48	33	77	78	88	37
60-64	113	207	37	29	94	108	57	42
65-69	72	107	25	13	74	63	49	27
70-74	29	37	24	5	34	45	33	15
75-79	16	18	9	1	15	20	11	14
80-84	5	4			9	3	8	5
85-89	1	1			3	1	1	2
90-94					0	1	0	2

occurred in patients whose ages were not over twenty years apart: 69.3 per cent of the male out-patient department cases occurred in patients between the ages of fifty and sixty-nine years of age, while 69.4 per cent of the females were between forty-five and sixty-four years of age inclusive. Among the ward patients with hypertension 61.8 per cent of the males and 61.7 per cent of the females were between fifty and sixty-nine years old. Up to fifty years of age there was little difference in the percentage age frequency curve for the two sexes, but after this age the frequency of hypertension in women increased more rapidly than in men.

It is necessary to compare the age distribution of these cases of hypertension with the ages of patients treated for other conditions. In order to do this there has been tabulated in Tables I-E and II the ages of the 1213 persons who were examined in the medical out-patient department during the month of March, 1929, and the ages of 1278 individuals who were admitted to the medical wards of the hospital during the months of April, August and December, 1927.

In the medical out-patient department 54.3 per cent of the male controls and 12.2 per cent of the male patients with hypertension were less than forty-five years old, while 66.9 per cent of the female controls and 16.4 per cent of the women with hypertension were of similar age. In the wards about 50 per cent of the controls and about 17 per cent of the patients with elevated blood pressure were less than forty-five years of age.

Figs. 1 and 2 show the curves for the age distribution of both control patients and patients with hypertension plotted in terms of the percentage of cases occurring in each five-year age period of life. The curve for women tends to be of the plateau type, while that for men shows a definite peak in the sixty to sixty-four year age group. Examination of the curves for hypertension shows two striking incisures, one in that for the male out-patient cases and the other in that for the female ward cases, both occurring in the fifty-fifth to fifty-ninth year group. If the age incidence is arranged for ten-year periods, as has been done in some of the reports discussed above, these incisures disappear. This might be interpreted to signify that five-year periods are too short for statistical significance. When the total cases are separated into two groups, the one representing uncomplicated hypertension and the other representing cases complicated by chronic nephritis, chronic myocarditis, or cerebral hemorrhage, age frequency curves are obtained essentially like those presented in Figs. 1 and 2.

RELATIVE FREQUENCY OF HYPERTENSION IN MEN AND WOMEN

Most writers on hypertension are of the opinion that hypertension is more frequently found among men. Table III is based upon all the data which we have found available on this subject. There are several reports in the literature on various aspects of hypertension and sphygmomanometry which have been based on analyses of fairly large groups of individuals. In Table III we have calculated the relative number of men and women with hypertension presented in each of these reports.

The relative incidence of hypertension found in the two sexes must necessarily have been influenced by the comparative numbers of men and women who presented themselves for examination. For example, Symonds[17] reported the blood pressure readings of over 162,000 holders of life insurance policies. Since 92.6 per cent of all these cases were men, it is not surprising to find that over 95 per cent of those discovered to have hypertension were of the male sex.

The determination of the relative frequency with which hypertension occurs in the two sexes should be based on the comparative frequency with which men and women with high blood pressure are found as a result of examining equal numbers of each sex. Wherever possible, we have attempted to reproduce this ideal situation by calculating what

TABLE III

SEX INCIDENCE OF HYPERTENSION

SOURCE		TOTAL CASES EXAMINED			CASES OF HYPERTENSION				
		Total Cases	Per Cent Men	Per Cent Women	Total Cases	Per Cent Men	Per Cent Women	Corrected for Sex Incidence in Total Cases	
								Per Cent Men	Per Cent Women
Gibes	(26)				90	65.6	34.4		
Kulbs	(25)		Not Given		288	59.7	40.3		
Keith, Wagener, Kernohan	(24)				81	59.3	40.7		
Cummings	(27)				150	44.0	56.0		
Bowes	(10)				150	33.3	66.7		
Alvarez, Wulzen, Mahoney	(3)	14,934	40.2	59.8	1,491	83.5	16.5	88.3	11.7
Bell and Hartzell	(13)	2,071	73.8	26.2	143	83.8	16.2	64.8	35.2
Symonds	(17)	162,356	92.6	7.4	9,001	95.3	4.7	61.9	38.1
Bell and Clawson	(14)	4,578	72.4	27.6	420	78.6	21.4	58.3	41.7
Gelman	(5)	3,761	70.2	29.8	344	74.2	25.8	54.9	45.1
Saller	(6)	4,128	57.8	42.2	685	33.8	66.2	27.2	72.8
Boston City Hospital		Control Cases							
O. P. D.	Total	28,906	47.8	52.2	1,620	27.8	72.2	29.5	70.5
Wards	Total	1,278	65.0	35.0	1,104	46.8	53.2	32.2	67.8
O. P. D.	Uncomplicated				1,387	23.9	76.1	25.7	74.3
Wards	Uncomplicated				384	39.9	60.1	26.3	73.7
O. P. D.	Complicated				233	47.3	52.7	49.5	50.5
Wards	Complicated				720	50.7	49.3	35.7	64.3

the result would be were the examination made in this manner. The results of these calculations appear in Table III under the column headed "corrected for sex incidence in total cases." As an illustration, let us again examine the data presented by Symonds.[17] As a result of the medical examination of this large group of accepted "life insurance risks," 8579 men (95.3 per cent) and 422 women (4.7 per cent) were discovered to have systolic blood pressures of 140 mm. Hg or over. The 162,356 "accepted risks" were made up of 92.6 per cent men and 7.4 per cent women. If these cases had been composed of equal numbers of each sex, there would have been 4,630 men with high blood pressure ($8579 \times \frac{50}{92.6}$) and 2850 women with hypertension ($422 \times \frac{50}{7.4}$). The cases with elevated blood pressures would then be made up of 61.9 per cent men and 38.1 per cent women.

The data of reports available in the literature show a wide variation in the relative frequency with which hypertension was found in the two sexes, regardless of whether one examines the actual number of hypertensives of each sex reported to have high blood pressure or whether one corrects the figures for the sex incidence shown by the total group examined. This variation may be due in part to the fact that the sources of these statistics are so different as to prevent ready comparison.

The medical out-patient records of the Boston City Hospital show a decided preponderance of female hypertensives over male. This is but slightly decreased when corrected for the relative numbers of men and women who make up the clientele of this section of the hospital. There were 28,906 control cases representing all the new patients who were admitted to the medical out-patient department during the forty-five months under consideration. The figures for the ward cases show hypertension to be more equally distributed between the two sexes, but when corrected for the sex incidence of the controls, the situation is found to be essentially the same as occurred in the medical out-patient department. The corrected figures from both of these sources showed that about 70 per cent of the cases of hypertension occurred in women while only about 30 per cent of the cases occurred in men. The figures of Saller[6] showed a similar sex distribution when calculated on the supposition that equal numbers of men and women were examined.

The Boston City Hospital cases can be separated into two groups: those complicated by chronic nephritis, chronic myocarditis, or cerebral hemorrhage; and those which showed none of these complications. When the statistics for the uncomplicated group are corrected according to the above method, it is found that 73.7 per cent of the ward cases and 74.3 per cent of the out-patient cases occurred in women. The group with complications showed the cases to be distributed more equally between the two sexes, but even here males do not predominate.

Arterial hypertension was present in 2.9 per cent of the total number of male patients, and in 6.6 per cent of the total number of female patients admitted to the medical out-patient department during the period under consideration.

The data presented above indicate that while high arterial blood pressure without functional or organic kidney damage may in rare instances be present in childhood, its occurrence among young adults is not an infrequent manifestation. The fact that the age incidence curve shows a sudden rise after the five-year period of forty-five to forty-nine in women and fifty to fifty-four in men, calls for special consideration. It has been suggested on the basis of morphological studies of the cardiovascular system (Janeway,[28] Volhard[29]), as well as on the basis of physiological observations (Weiss and Ellis[30]), that in the causation of high blood pressure increased peripheral resistance plays an important rôle. Suggestive evidence is also available that this increased resistance, at least in one group of patients, is caused by the contracted state of the arterioles (Ellis and Weiss[31]). The more exact mechanisms which lead to this increase in the peripheral resistance are not known at present, although clinical observations and experiments on animals clearly indicate that several mechanisms may be responsible for elevated arterial blood pressure.

The coincidence of a great increase in the occurrence of hypertension with onset of the involutionary changes in the body suggests a correlation between the two conditions. Two interpretations may be offered in explanation of this: (1) It is possible that high blood pressure exists symptomless in the same individuals in early life, but only with the onset of involutionary changes becomes manifest in symptoms and signs. (2) It is also possible that simultaneously with the onset of involution, changes occur in the organs, including those of internal secretion, which regulate the blood pressure. As a result the blood pressure becomes elevated.

Although it is certain that the first interpretation explains a number of cases, the available statistical data on groups of persons considered normal indicate that the age incidence does not increase essentially until the beginning of involution, when it increases markedly. The correlation between involution and high blood pressure, therefore, cannot be denied, although a more precise definition of the exact nature of this correlation cannot be offered at present.

SUMMARY AND CONCLUSIONS

1. The curve of age incidence of out-patient and ward patients with hypertension in the Boston City Hospital shows a gradual and progressive rise up to the age period of forty to forty-five years. After the age period of forty to forty-five there is a sudden rise in the curve. After the age of seventy, the incidence drops sharply. Over 60 per cent of

the cases occurred in patients between the ages of forty-five and sixty-nine inclusive.

2. The onset of the steep rise in the age incidence curve of hypertension occurs almost five years earlier for women forty-five to forty-nine years) than for men (fifty to fifty-four years).

3. Hypertension was present more frequently among female than among male patients of the Boston City Hospital. It occurred in 2.9 per cent of the total number of male, and 6.6 per cent of the total number of female patients admitted to the medical out-patient department during the period under consideration.

4. The fact that a sudden rise in the age incidence of hypertension occurs at a time in each sex which coincides with the age at which involution of the male and female glands of internal secretion and other organs begins, suggests the possibility of an etiological relationship between involutional changes of the human body and a group of patients with hypertension.

REFERENCES

1. Amberg, S.: Hypertension in the Young, Am. J. Dis. Child. **37:** 335, 1929.
2. Alvarez, W. C.: Surprising Frequency of Hypertension in a Group of Young Drafted Men, Calif. State J. Med. **17:** 367, 1919.
3. Alvarez, W. C., Wulzen, R., Mahoney, L. J.: Blood Pressure in Fifteen Thousand University Freshmen, Arch. Int. Med. **32:** 17, 1923.
4. Diehl, H. S., and Sutherland, K. H.: Systolic Blood Pressures in Young Men, Arch. Int. Med. **36:** 151, 1925.
5. Gelman, J.: Hypertoniestudien, II Mitteilung, Alters- und Berufsverschiebungen im hämodynamischen System, Ztschr. f. klin. Med. **106:** 310, 1927.
6. Saller, K.: Ueber die Altersveränderungen des Blutdrucks, Ztschr. f. d. ges. exper. Med. **58:** 683, 1928.
7. Moog, O., and Voit, K.: Klinische Beobachtungen an Jugendlicher Hypertonikern, Münch. med. Wchnschr. **74:** 9, 1927.
8. Magniel, M.: L'Hypertension Arterielle du Jeune Age, Paris Méd. **53:** 229, 1924.
9. Wildt, H.: Ueber Blutdruck im Greisenalter, Zentralbl. f. Herz. u. Gefässkr. **4:** 41, 1912.
10. Bowes, L. M.: Blood Pressure in the Aged, J. Lab. & Clin. Med. **2:** 256, 1917.
11. Richter, A.: Ueber Blutdruck im Höheren Lebensalter, Deutsche Arch. f. klin. Med. **148:** 111, 1925.
12. Shaw, H. B.: Hyperpiesia and Hyperpiesis, London, 1922, Oxford Med. Pub.
13. Bell, E. T., and Hartzell, T. B.: Studies on Hypertension, J. M. Research **44:** 473, 1924.
14. Bell, E. T., and Clawson, B. J.: Primary Hypertension, Arch. Path., **5:** 939, 1928.
15. Van Wagenan, G. A.: Average Systolic Pressure of Accepted and Declined Risks, Proc. A. Life Insur. M. Dir. Am. p. 245, 1913.
16. Fisher, J. W.: Further Report of the Diagnostic Value of the Systolic Blood Pressure, Proc. A. Life Insur. M. Dir. Am. p. 203, 1915.
17. Symonds, B.: The Blood Pressure of Healthy Men and Women, Proc. A. Life Insur. M. Dir. Am. **9:** 22, 1922.
18. Osler, W.: Principles and Practice of Medicine, New York, Ed. 10, 1926, D. Appleton and Co.
19. Fisher, J. W.: Report of Blood Pressure Committee, Proc. A. Life Insur. M. Dir. Am. **9:** 59, 1922.
20. Frost, H. M.: Hypertension and Longevity, Bost. Med. and Surg. J. **193:** 241, 1925.
21. Dublin, L. I., Fisk, E. L., and Kopf, E. W.: Physical Defects as Revealed by Periodic Health Examinations, Am. J. M. Sc. **170:** 576, 1925.

22. Rogers, O. H., and Hunter, A.: Mortality Study of Impaired Lives, Proc. A. Life Insur. M. Dir. **13**: 176, 1926.
23. Weitz, W.: Zur Ätiologie der genuinen oder vasculären Hypertension, Ztschr. f. klin. Med. **96**: 151, 1923.
24. Keith, N. M., Wagener, H. P., and Kernohan, J. W.: The Syndrome of Malignant Hypertension, Arch. Int. Med. **41**: 141, 1928.
25. Kulbs, F.: Ueber die Hypertonien, Deutsche med. Wchnschr. **48**: 717, 1922.
26. Gibbes, J. H.: Analysis of One Hundred Cases of Hypertension, Southern M. J. **19**: 413, 1926.
27. Cummings, R.: Study of One Hundred and Fifty Cases of Hypertension, Calif. State J. Med. **17**: 373, 1919.
28. Janeway, T. C.: A Clinical Study of Hypertensive Cardiovascular Disease, Arch. Int. Med. **12**: 755, 1913.
29. Volhard, F.: Der arterielle Hochdruck, Verhandl. deutsch. Gesellsch. Inn. Med. **35**: 134, 1923.
30. Weiss, Soma, and Ellis, L. B.: The Dynamics of the Circulation in Hypertension and Its Bearing on Therapy, J. Clin. Investigation **7**: 490, 1929.
31. Ellis, L. B., and Weiss, Soma: The Measurement of Capillary Pressure Under Natural Conditions and After Arteriolar Dilatation in Normal Subjects and in Patients with Arterial Hypertension and with Arteriosclerosis, J.

THE DISTORTION OF THE ELECTROCARDIOGRAM BY CAPACITANCE*

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WHEN the General Electric Company first developed the amplifier tube as a method of recording the electricity of the heart, tests were made by H. B. Marvin of the General Engineering Laboratory

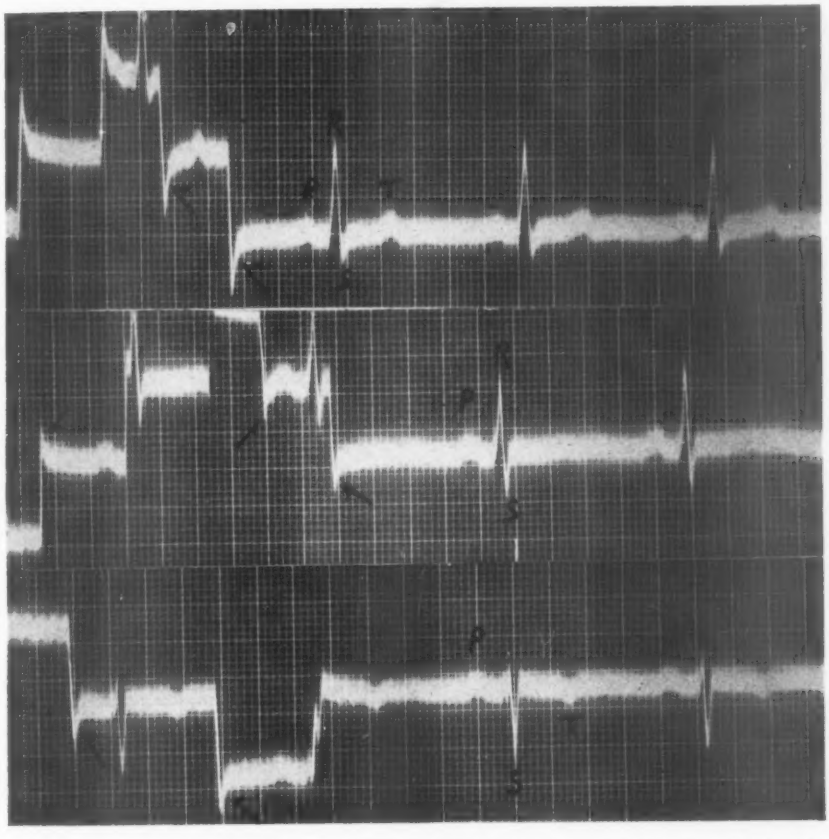

Fig. 1.—Record taken with the string galvanometer on a patient with high resistance. Comparing with Fig. 2, note the considerable overshooting at the test of standardization, the larger amplitude of QRS and T-waves than in Fig. 2.

of the General Electric Company, Schenectady, in conjunction with me, of the ability of this instrument to record the action current of the human heart. At the New York Hospital records were taken of

*From the Cornell University Medical School and the Second Medical Division of New York Hospital.

numerous patients, first with a large model of the Williams-Hindle electrocardiograph, and then with the instrument which had been devised in the General Electric Laboratory. These records were in all respects identical, and they were shown to the medical profession at the meeting of the American Medical Association at Atlantic City in June, 1925. Following this I had an opportunity to use one of these instruments before they were placed on the market, and my experience with it led me to believe that the records which it produced were identical with the records obtained from the same heart by the string

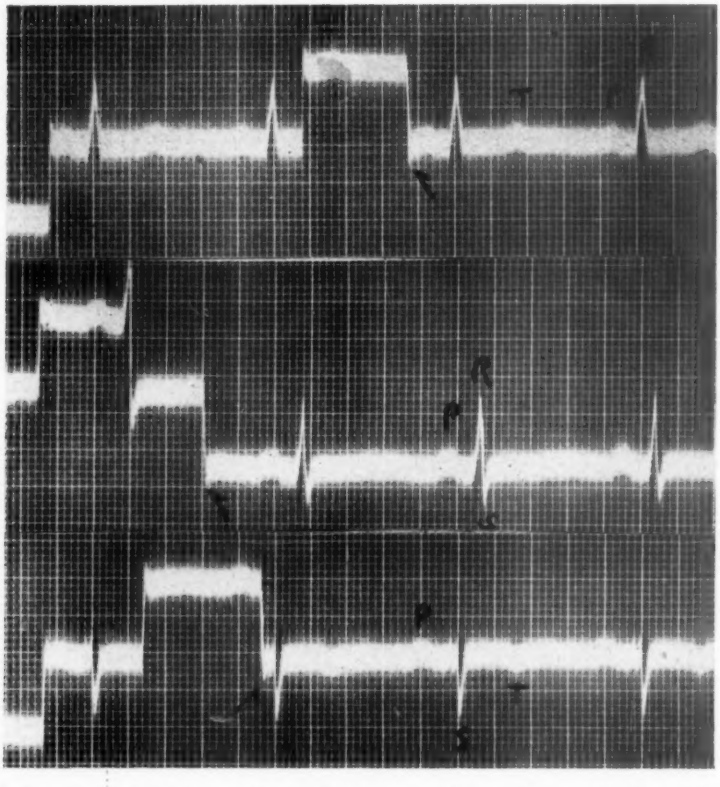

Fig. 2.—Record of the same patient with low resistance taken with the string galvanometer.

galvanometer type of instrument when the resistance of the patient was low. It was observed that with the amplifier tube instrument no distortion of the curve resulted from a high resistance of the skin of the patient, as occurred when using the string galvanometer. If a record was obtained from a patient by means of the string galvanometer, and owing to high skin resistance the overshooting was great, a record obtained from the same wires, without changing the electrodes but using the radio amplifier tube instrument, would show no evidence of overshooting.

Fig. 1 is the record of a patient taken with the string galvanometer. The resistance in the three leads, as measured by substitution, was 3900 ohms for Lead I, 5700 ohms for Lead II, and 7000 ohms for Lead III. It will be seen in the control of standardization that there is marked overshooting after the test current is applied, and it will be seen in the record that there is a distortion due to this. This record should be compared with Fig. 2 which was taken with the same instrument, with the resistance in all three leads 2000 ohms. There is but the slightest overshooting after the jump, due to the standardization test in this record, and the different appearance of the curve is evident;

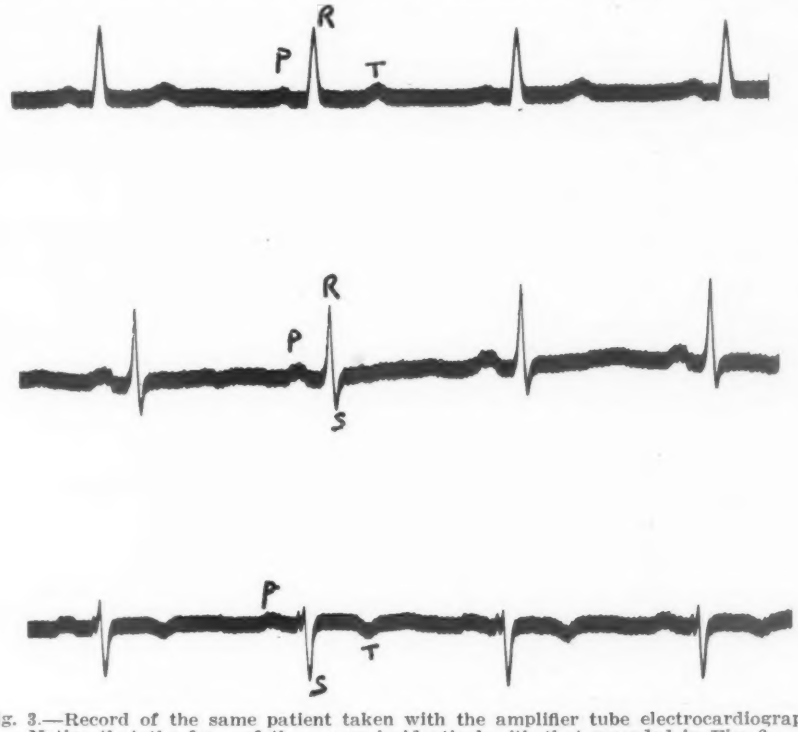

Fig. 3.—Record of the same patient taken with the amplifier tube electrocardiograph. Notice that the form of the waves is identical with that recorded in Fig. 2.

there is no S-wave in Lead I as is seen in Fig. 1; the amplitude of the R-wave is less in this lead, as is also the amplitude of the T-wave. Fig. 3 is a record taken from the same patient with the amplifier tube instrument immediately after the record in Fig. 1 was taken, and while the resistance of the patient was still high; the electrodes were not disturbed, but the lead wires were changed from one galvanometer to the other. It will be seen that this curve shows no evidence of distortion such as is seen in Fig. 1; it closely resembles Fig. 2. Fig. 4 is a record, taken with the string galvanometer, of another patient whose resistance was very high, Lead I measuring over 10,000 ohms, Lead II measuring 9000 ohms, and Lead III over 10,000 ohms. Fig. 5 is a record of

the same patient taken with the amplifier tube instrument as described above, immediately after Fig. 4 was obtained. It is seen that there is no evidence of overshooting in this record; the amplitude of the QRS group is less and is probably normal for this patient; the overshooting indicated at the point of the arrows in Fig. 4 is not present.

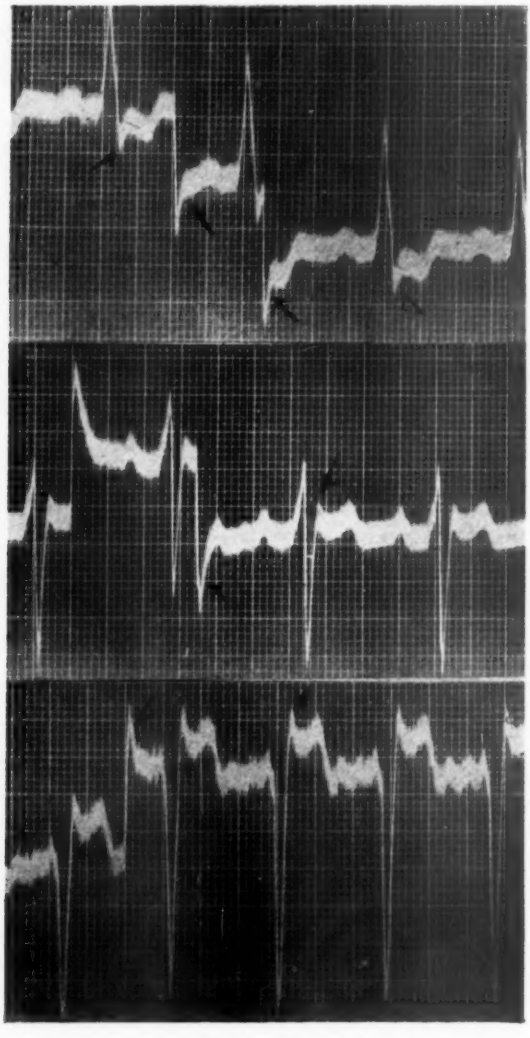

Fig. 4.—Record taken with the string galvanometer of a patient with very high resistance. Note the overshooting after the standardization jump, the large amplitude of QRS group and overshooting after the R-wave in Lead I and after the S-wave in Leads II and III.

This seems to be one of the obvious advantages of this type of instrument, and so it was with great surprise that I observed an article in the AMERICAN HEART JOURNAL, October, 1928,[1] in which it was claimed that overshooting is recorded by the amplifier tube instrument

—in fact that it is an integral part of all records by this instrument, so that for the purpose of examining the exact form of the electrocardiographic waves this instrument is useless.

It is an interesting fact that the record in Fig. 4 of the above article shows something which looks very much like the distortion due to overshooting in the last two complexes of the record. It seems to me that from the evidence presented by the author, his conclusion is quite unjustified; in fact, it seems that this conclusion is incorrect for reasons which will be presented. First, assuming that the overshooting in the records taken with the string galvanometer is due to capacitance,

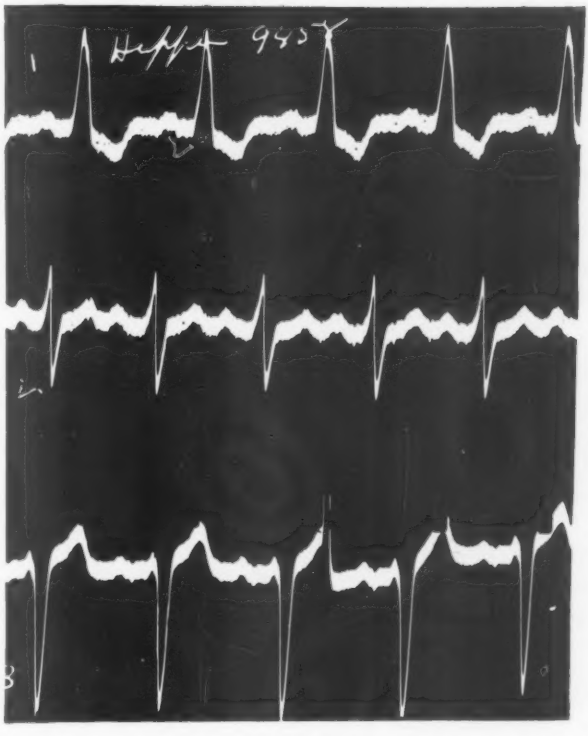

Fig. 5.—Record of the same patient with the amplifier tube instrument. Note the small size of the QRS group, and the absence of overshooting after the R- and S-waves.

there must be a flow of current to be impeded by the capacity resistance. In the string galvanometer there is a flow of current, but in the circuit of the patient and the amplifier tube there is no such flow of current,* the instrument being really a potentiometer. Since there is no flow of current, there can be no charging up of capacity; and therefore the overshooting which with the string galvanometer is due to the charging up of capacity, cannot occur. Second, a patient has

*There is a shunt of 900,000 ohms across the patient's circuit, but this resistance is so high that the flow of current is practically nil.

been found whose electrocardiogram shows a very sharp, almost right-angled turn from the R-wave into the beginning of the T-wave, as will be seen in Fig. 2, Lead I. The slightest overshooting would become apparent as the appearance of a small S-wave or at least some downward deflection following the R-wave. A record taken with the General Electric instrument is shown in Fig. 3, and it will be seen that not only are the waves of the same height and form in these two figures, but at this critical point the R-wave turns into the T-wave without the slightest evidence of overshooting; in fact, exactly as it does in the record taken with the string galvanometer.

Dr. Dock has compared these two types of instrument as if they depended upon the same electrical principles for their operation; this has given rise to the error into which he has fallen. The apparent overshooting in the standardization curve of the Victor instrument is easily explainable when one inquires into how this deflection is produced. The current which gives rise to this deflection is drawn from the same battery which charges the filaments of the amplifying tubes; this slight drain of current from the battery gives rise to a slight fall in the charge upon the filament, and accordingly a difference in potential between the filament and the grid of the tube is set up, which produces the movements of the indicator in question.* It would be impossible for a similar distortion of the electrocardiogram to occur while taking the patient's record, because the current which activates the galvanometer at that time is drawn from the patient and not from the battery which charges the filament. It is impossible to say what gave rise to the distortion of the current which was observed by Dr. Dock, but it seems impossible in view of the above that it could have the origin to which he ascribes it. The new instrument has certain advantages and disadvantages in comparison with the old; but since none of the disadvantages are vital to the obtaining of a correct record, it seems necessary to deny this erroneous statement which might throw the apparatus into unwarranted disuse.

REFERENCE

1. Dock, Wm.: The Distortion of the Electrocardiogram by Capacitance 4: 109, 1928.

*This, it will be seen, is an entirely different electrical process from that which gives rise to the overshooting with capacity resistance in the string galvanometer circuit.

THE TREATMENT OF ADAMS-STOKES SYNDROME DUE TO AURICULOVENTRICULAR BLOCK*

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THE treatment of Adams-Stokes syndrome due to auriculoventricular block is in the vast majority of cases so unsatisfactory that any therapeutic measure which appears to afford a reasonable prospect of success is well worthy of a trial. The striking success following the administration of barium chloride in a case of very exceptional severity, in which other measures had completely failed, suggests that this drug should invariably be tried in this condition; and the satisfactory result following the exhibition of barium chloride by mouth together with adrenalin hydrochloride hypodermically in a case of moderate severity in which the administration of barium chloride alone was quite ineffective is also of considerable therapeutic importance.

We propose to deal with the subject in the following order: (1) Some general observations regarding the pathogenesis of Adams-Stokes syndrome. (2) The aim and the rationale appertaining to any therapeutic measure. (3) The rationale and the comparative value of various therapeutic measures, including barium chloride and adrenalin.

THE PATHOGENESIS OF ADAMS-STOKES SYNDROME

Adams-Stokes syndrome occurring in auriculoventricular block is due to temporary anemia of the brain, the result of bradycardia. The attacks may occur under one of the following conditions: (1) Suddenly developed, transient, complete auriculoventricular block. Several cases of this kind have been reported. The conduction of the stimulus for contraction along the auriculoventricular junctional tissues is normal except that there is a liability to transient interruptions. Lewis[1] is of opinion that such transient interruptions may occur in cases in which there is a lesion of the auriculoventricular junctional tissues. Cohn, Holmes and Lewis[2] have reported a case in which the fibers of the auriculoventricular bundle were found on post-mortem examination to be separated by large venous sinuses; the intermittent swelling of which, they considered, was responsible for the attacks. (2) Partial heart-block in which there occurs either an intermittent period of complete heart-block, resulting in a temporary standstill of the ventricles, or, rarely, merely a temporary increase in the grade of the partial heart-block, resulting in a temporary increase in the degree of the bradycardia. (3) Complete heart-block in which the con-

*From the National Hospital for Diseases of the Heart.

dition has become permanently established, especially if the ventricular rate is below 30 per minute. In these cases pauses of unusual length, due to temporary standstill of the ventricles, the result of diminished irritability of the ventricles, may occur. Taking cases as a whole, Adams-Stokes syndrome is most commonly met with in patients with a severe grade of partial heart-block in whom complete block is developing. When complete heart-block has become permanently established, the ventricles apparently tend to become accustomed to the condition, and the pauses of unusual length referred to are not so likely to occur. One or more of the three following morbid affections may be responsible for the bradycardia which causes the Adams-Stokes syndrome in auriculoventricular block, namely: (1) a gross lesion of the auriculoventricular junctional tissues—sclerotic, less frequently gummatous, or, rarely, acute inflammatory; (2) overaction of the vagus; (3) diminished irritability of the ventricular myocardium.

THE AIM AND THE RATIONALE APPERTAINING TO ANY THERAPEUTIC MEASURE

The aim of any therapeutic measure is to increase the ventricular rate. Resolution of the auriculoventricular junctional lesion is only possible in cases of gummatous infiltration and acute inflammatory changes, and in the latter it is the usual sequel. In view of the facts that sclerotic changes account for the majority of cases in which there is a lesion of the auriculoventricular junctional tissues and that resolution of sclerotic changes is not possible, it naturally follows that attention should be directed to any other possible factor or factors which may be partly responsible for the bradycardia. In this connection, in partial heart-block, the indication is to counteract any possible vagal overactivity which may tend to increase the degree of existing block; while in both partial and complete heart-block the indication is to increase stimulus production, excitability and contractility of the heart muscle itself, with the object of preventing temporary ventricular standstill, or, if such should occur, of diminishing its duration.

THE RATIONALE AND THE COMPARATIVE VALUE OF VARIOUS THERAPEUTIC MEASURES

Antisyphilitic Measures.—A number of cases have been recorded in which appropriate and adequate antisyphilitic treatment appears to have been rewarded with recovery. These are cases in which the auriculoventricular block is the result of gummatous infiltration.

Potassium Iodide.—It may be worthy of note that when the cause is other than syphilis, potassium iodide, by its depressing effect on the ventricular muscle, may even aggravate the complaint, as in one of the cases reported by Herrmann and Ashman,[3] and in a case observed by Strauss and Meyer.[4]

Thyroid.—Because the administration of thyroid extract causes tachycardia in the normal heart, which they thought was probably due

either to stimulation of the sympathetic nerves or to direct stimulation of the sinus node, and also because in thyrotoxic hearts there is irritable and rapid cardiac action, with concomitant myocardial degeneration, Blackford and Willius[5] administered large doses of thyroxin, the active principle of the thyroid gland, to four patients who were subject to Adams-Stokes syndrome due to complete auriculoventricular block. In each case there was an increased ventricular rate, cessation of the attacks, and a marked improvement in nutrition. They attributed this to thyroxin directly increasing the idioventricular rate. Later, however, Aub and Stern[6] reported a case of complete heart-block without Adams-Stokes syndrome, in which the administration of large doses of thyroid had no influence on the ventricular rate, although the rate of the auricles was materially increased. Willius[7] after further investigation came to the conclusion that the beneficial effect of thyroid extract in patients subject to Adams-Stokes syndrome is not due, as he originally thought, to an increase in the idioventricular rate, but to what he described as an increased circulation rate and a consequent improved blood supply; the former being the result of increased metabolism causing an augmentation of the volume output of the blood for each beat and a relatively dilated arteriocapillary system. Drake[8] has recently reported a case of complete auriculoventricular block with Adams-Stokes syndrome in which the administration of thyroid extract at first caused a temporary resumption of normal rhythm; but a second trial of the drug resulted in alternating periods of 2:1 partial block and complete block. In this case, therefore, the drug does not appear to have been of any permanent value in reducing the frequency of the Adams-Stokes attacks, and its administration was ultimately stopped, because of nausea.

Atropine.—Since the action of atropine is to paralyze vagal activity, its employment is only likely to prove successful when Adams-Stokes syndrome depends upon overaction of the vagus. It has been demonstrated in man, by the employment of graphic methods, that stimulation of the vagus, by means of compression in the neck, by the act of swallowing, or by pressure upon the eyeball, may, by diminishing conductivity of the auriculoventricular junctional tissues, induce a transient heart-block, which is abolished by atropine. It has been shown further that stimulation of the vagus by these methods may, in the same way, induce a temporary increase in the degree of a preëxisting heart-block. The digitalis series of drugs also may, by their action on the vagus, produce a condition of heart-block, which is abolished by the administration of atropine. It should be noted, however, that persistent block of a severe grade is not vagal in the vast majority of cases, since it is unaffected even by full doses of atropine. This is confirmed by experimental work on dogs by several workers (Erlanger and Hirschfelder,[9] Fredericq,[10] Kahn,[11] van Egmond[12]). They showed

that in a heart in which the auriculoventricular bundle was destroyed, stimulation of the vagus no longer exercised any influence on the ventricles. They regard this as probably due to the fact that in some part of the course of the auriculoventricular tissues the pathway of the branches of the vagus nerve must have been broken. It is possible, therefore, that in Adams-Stokes syndrome due to partial heart-block, atropine may sometimes be of service by paralyzing vagal overactivity and so improving conductivity of the auriculoventricular junctional tissues. Hirschfelder has suggested that atropine may also improve the nutrition of the auriculoventricular tissues, by increasing the velocity of the circulation. In the case of Adams-Stokes syndrome due to complete heart-block, atropine is totally ineffective; indeed, it may even aggravate the complaint, as in a case of Cohn and Levine,[14] and in a case of Herrmann and Ashman,[3] in both of which the administration of the drug was followed by an increase in the rate of the auricles, without any corresponding increase of conductivity and of the ventricular rate, so that the relative degree of block was actually increased.

The Digitalis Series of Drugs.—When Adams-Stokes syndrome occurs in patients with partial heart-block, the administration of digitalis is contraindicated, since in these cases digitalis only increases the degree of the existing block. Heart-block produced by digitalis is usually due to stimulation of the vagus and is generally abolished by the exhibition of atropine. Cases do occur, however, in which atropine has no effect; in such cases the block must be attributed to a direct action of the drug on the auriculoventricular junctional tissues. When Adams-Stokes syndrome occurs in cases of complete heart-block, digitalis may be of value by increasing the excitability and contractility of the heart muscle, and so increasing the ventricular rate; indeed, Tabora[15] and Erlanger[16] found that in cases of experimentally produced complete heart-block digitalis caused a gradual increase in the ventricular rate to double its former level. The observations of these two workers were confirmed by van Egmond,[12] and by Rothberger and Winterberg,[17] who observed that digitalis increases the rate and force of the contractions of the ventricles, and in large doses may even induce paroxysms of premature contractions, which may terminate in ventricular fibrillation.

Caffein and Theobromin.—Van Egmond[12] found that in experimentally produced complete heart-block, the administration of caffein caused a transient increase in the rate and force of the ventricular contractions. It has also been found experimentally that diuretin, a compound of theobromin and sodium salicylate, has the effect of dilating the coronary arteries, thus improving the nutrition of the heart muscle. Notwithstanding these observations, Hirschfelder[13] is of opinion that caffein and theobromin are of no value in Adams-Stokes syndrome.

The Nitrites.—Strauss and Meyer[4] observed in a case of transient heart-block with Adams-Stokes attacks that nitroglycerin caused an increase in the pulse-rate for a short period. The drug, however, had no influence in preventing the recurrence of the attacks. These observers are of opinion that because of the vascular dilatation produced by nitroglycerin, there is an automatic increase in the pulse-rate in order to maintain an efficient circulation. In their case, nitroglycerin appeared to be more effective when the patient was under the influence of barium chloride. We cannot say that we have ever found the nitrites of any value.

Adrenalin.—Within recent years, a number of cases have been recorded in which the treatment of Adams-Stokes syndrome by adrenalin has been followed by gratifying results. The effect of the drug is usually to increase the rate of the heart, by stimulating the sympathetic nerve endings in the cardiac muscle. It also stimulates the vagal inhibitory center, and, if the vagal tone is good, this may result even in an actual slowing of the heart (Meek and Eyster,[18] Hoskins and Lovette,[19] and Korns and Christie[20]). Most observers (Cushny,[21] Hirschfelder[13]) are of the opinion that the drug also has the effect of dilating the coronary arteries, with resultant improvement of the nutrition of the myocardium. In a heart in which the auriculoventricular bundle has been destroyed, stimulation of the sympathetic—unlike stimulation of the vagus—has still a definite influence upon the rate of the ventricles (H. E. Hering[22]). The administration of adrenalin should, therefore, be followed by an increase in the ventricular rate. Such was noted by Cullis and Tribe,[23] who, working on cats and dogs, demonstrated that small doses of the drug caused an increase in the rate and force of the contractions of the auricles and ventricles, both before and after section of the auriculoventricular bundle. Other observers (van Egmond,[12] Routier,[24] Hardoy and Houssay,[25] and Clerc and Pezzi[26]) agree that the administration of adrenalin after the induction of experimental complete heart-block causes an acceleration of both the auricular and ventricular rates and also the occurrence of premature ventricular contractions. Kahn[27] found that when injected intravenously into dogs adrenalin produced heart-block. Routier,[24] on the other hand, actually noted a temporary disappearance of an experimentally produced heart-block after the exhibition of a moderate dose of adrenalin. He attributed this to the stimulation of the sympathetic nerve endings in the auriculoventricular bundle resulting in improved conductivity. This observation, however, has not been confirmed by any other experimental workers.

The *clinical* effect of adrenalin in cases of Adams-Stokes syndrome appears to have first been described in 1916 by Danielopolu and Danulescu,[28, 29] who employed it in a case of complete heart-block and also in a case of partial heart-block. In both cases there was an increase in the auricular and ventricular rates and also the occurrence of pre-

mature ventricular contractions. The partial heart-block was abolished, but the complete block was unaffected. Later, Strisower[30] reported a case of complete heart-block in which the injection of adrenalin, 0.5 c.c. of $\frac{1}{1000}$ solution, was followed by an increased ventricular rate and a temporary return to the normal rhythm. A month later the patient exhibited 2:1 auriculoventricular block, which was abolished, but only for a few seconds, by a further exhibition of adrenalin. More recently, Parkinson and Bain[31] described a case showing varying degrees of partial heart-block, in which adrenalin facilitated conductivity when partial block was present but had no effect when the block was complete. Several other observers (Arrilaga,[32] Lutembacher[33]) have noted an increase in the auricular and ventricular rates, together with premature ventricular contractions, without, however, any alteration in the degree of block. Lutembacher[33] further noted that after an initial acceleration there was a slowing of the auricular and ventricular rates. Phear and Parkinson,[34] Feil,[35] and others, have reported cases in which the temporary standstill of the ventricles determining the attacks was abolished—without, however, any change either in the usual heart rate or in the degree of the existing block—with consequent abolition of the Adams-Stokes attacks. Korns and Christie,[20] on the other hand, described a case of 2:1 heart-block, in which treatment by adrenalin resulted in an increase in the degree of the block, although there was a coincident increase in the auricular and ventricular rates. They attributed the increase in the degree of the block to central vagus effects.

It is thus seen that both experimentally and clinically adrenalin may prevent a temporary standstill of the ventricle, by increasing the ventricular rate; it may improve conductivity and thus lessen the degree of any existing partial heart-block and exceptionally may even temporarily restore normal rhythm in complete heart-block; and it may produce premature contractions. It should be noted, however, that when vagal tone is good, the drug may occasionally, by its central vagal effect, increase the degree of existing block and may also increase the rate of the auricles out of proportion to the increase in the rate of the ventricles. Nevertheless, because of its action in the great majority of cases, it is indicated in cases of Adams-Stokes syndrome due to auriculoventricular block, especially during an actual attack.

The great disadvantage of adrenalin is that its action is of very short duration; therefore, the drug is not often effective when employed in the intervals between the attacks with the object of preventing their recurrence. When used for this purpose, it may be administered either subcutaneously or intramuscularly, in a dosage of from 5 to 10 minims of $\frac{1}{1000}$ solution thrice daily. Adrenalin is, however, the only potent therapeutic measure at our disposal during an actual attack. It is necessary to point out that when—as in the vast majority

of cases—the attack is due to a temporary standstill of the ventricles, with consequent temporary cessation of the circulation, intracardiac injection is necessary, because the beneficial effect of the drug is due to its action in stimulating the sympathetic nerve endings in the heart muscle. The dose should be 0.5-1 c.c. of $\frac{1}{1000}$ solution. In the rare cases in which the attacks are due to merely a temporary increase in the grade of an existing partial heart-block, the drug may be effective even if given subcutaneously or intramuscularly.

Ephedrin.—Ephedrin has recently been employed as a substitute for adrenalin. It is the active principle isolated from the plant Ma Huang, which has been used as a medicine by the Chinese since antiquity. The chemical composition of ephedrin is closely allied to that of adrenalin, and the drug has a similar pharmacological action. It differs from adrenalin, however, in that its effect persists for several hours; and, moreover, it has the great advantage of being effective when administered orally. The first case in which ephedrin was employed in auriculoventricular block was one reported by Miller.[36] There was complete heart-block but no history of Adams-Stokes attacks. A moderate rise of blood pressure, an increase of both the auricular and ventricular rates—without, however, affecting the degree of the auriculoventricular block—and changes in the shape of the ventricular complexes followed the administration of the drug. Stecher[37] has recently reported favorably of the employment of ephedrin in a case of complete heart-block with Adams-Stokes syndrome. Although the exhibition of barium chloride resulted in some degree of improvement, the attacks still continued. Ephedrin was then administered, by mouth, in doses of 30 mgm. thrice daily for one week, followed by 20 mgm. thrice daily for two weeks. There was a complete absence of attacks during the administration of the drug, and afterward for a further ten weeks during which the patient was under observation. The highly successful result in this case would strongly suggest that further investigation of this drug is advisable.

Barium Chloride, and Barium Chloride Together With Adrenalin.—The value of barium chloride in the treatment of Adams-Stokes syndrome is due to the action which the drug has in increasing the irritability of the heart muscle. It has a characteristic action on many forms of muscular tissue, i.e., the contractions become stronger and very greatly prolonged. Junkemann[38] observed that the frog's heart at first beats more strongly and its rate is diminished; later it develops a rapid, irregular, idioventricular rhythm; and finally it stops in systole. Boehm[39] noted that in the case of mammals moderate doses of the drug cause an acceleration of the ventricular rate and an increase of blood pressure, but that large doses bring about a standstill of the left ventricle in systole. Ringer,[40] Brodie and Dixon,[41] Magnus,[42] and others agree with the findings of both these observers. It is be-

lieved that since its action is unaffected by curara, the drug acts directly upon the contractile substance of the muscle and not upon the nerve endings. Rothberger and Winterberg[43] carried out a series of detailed experiments on dogs concerning the action of barium chloride and calcium chloride, controlling their findings by means of the electrocardiograph. They found that both drugs increase the irritability of the cardiac muscle. After the administration of 5-10 mgm. of barium chloride intravenously, the heart could no longer be brought to a standstill by a simultaneous stimulation of the sympathetic and vagus nerves, which is the case in the normal heart. After 25-50 mgm. were administered, stimulation of the sympathetic, either directly or by means of adrenalin, caused the ventricular rate to be increased and also the occurrence of runs of ventricular premature contractions. With 50-100 mgm., the runs of premature contractions occurred spontaneously. They ceased in 5-10 minutes; but they could be readily evoked again, either by direct stimulation of the sympathetic, or by stimulation with small doses of adrenalin or nicotine. The diverse appearance of the electrocardiograms indicated that the ventricles had been stimulated at numerous points. With still larger doses of barium chloride, ventricular fibrillation ensued. Practically the same results are obtained when calcium chloride is employed, but larger doses of this drug are necessary. The contractility of the heart muscle is increased, and the blood pressure is raised 10-20 mm. of mercury by both drugs. The rate of the auricles is increased, but to a less extent than in the case of the ventricles. These workers are of opinion that barium chloride has no notable effect on the sino-auricular node, or on the auriculoventricular node. Van Egmond,[12] in cases of heart-block experimentally produced in dogs, confirmed the conclusions of Rothberger and Winterberg.[43] The importance of the foregoing observations lies in the fact that they show that barium, and, to a less degree calcium, increase the ventricular rate, either by stimulating the excitability of the existing idioventricular pacemaker, or by calling into action new ectopic ventricular foci. This may be produced by barium alone if used in a moderately large dosage; but stimulation of the sympathetic—which may be readily obtained by the administration of a small dosage of adrenalin—is also necessary if only a comparatively small dosage of the drug is used. In the treatment of Adams-Stokes syndrome, therefore, barium chloride alone, or barium chloride in combination with adrenalin, may be expected to be of definite therapeutic value.

The earliest clinical case of Adams-Stokes syndrome treated by barium chloride was reported by Wilson and Herrmann.[44] This was one of transient complete auriculoventricular block, thought possibly to be due to transient engorgement of large blood sinuses in the auriculoventricular node. At the suggestion of S. A. Levine,[14] the drug was

administered, in doses of ½ gr. ter in die, for a period of 38 days (May 18 to June 24), but without any effect in preventing the recurrence of the attacks. Shortly afterward, Cohn and Levine[14] reported the effect of the administration of barium chloride in three patients suffering from frequent Adams-Stokes syndrome. The usual therapeutic measures, including adrenalin, in each case failed to prevent the recurrence of the attacks, but barium chloride given orally proved successful. The following is a brief account of these cases.

CASE 1.—Male. Aged 55 years. A case of exceptional severity. The patient's condition had been steadily becoming worse until the administration of the drug was commenced. He was continually passing in and out of attacks of syncope, being conscious only about half the time, his condition resembling that of status epilepticus. The day following, although complete auriculoventricular block still persisted, there was an absence of long pauses and of attacks. Only 30 mgm. three times daily for two days were exhibited. The patient remained free from attacks for some weeks. After leaving the hospital, he began again to have frequent attacks. Calcium lactate, 1 gr. ter in die, was given, and the attacks ceased. Sudden death, however, occurred ten months after the commencement of barium chloride.

CASE 2.—Male. Aged 32 years. A case of moderate severity. Thirty mgm. of barium chloride four times daily for four days, after which 15 mgm. four times daily for three days, i.e., a total of 660 mgm., was exhibited. Together with the barium chloride, adrenalin, 0.3 c.c., was administered subcutaneously, four times daily for two days; after which it was reduced to 0.2 c.c. four times daily during the remainder of the time. After the commencement of the drugs, the patient had only one slight attack (on the seventh day), and more than a year after his discharge from hospital he was reported to have remained free from attacks and to be in excellent health.

CASE 3.—Female. Aged 52 years. A case of very considerable severity. Thirty mgm. of barium chloride ter in die was administered for nine days, i.e., a total of 810 mgm. This was followed by an interval of ten days, during which time the patient was discharged. The drug was then resumed, in the same dosage, for 10 days. The patient had remained free from attacks during this time. There was, however, a recurrence of the attacks, more severe than previously, ten days after cessation of the second course. The patient was readmitted to hospital and was kept alive by injections of adrenalin for about 20 days. At the end of this time barium chloride was resumed in doses of 30 mgm. four times daily for 44 days. It was then omitted for 36 days and during the whole of both these periods the patient remained free from attacks. She was then discharged from hospital, and the drug was continued for seven days, after which it was taken irregularly. The patient died suddenly seven months after the commencement of treatment by barium chloride and about three weeks after the discontinuance of regular doses of the drug.

Later, Levine[45] published a communication in which he stated that he had received information from two physicians to the effect that they had found that barium chloride was successful in preventing the recurrence of frequent Adams-Stokes attacks. A further case was reported by Levine and Matton,[46] in which, after the administration of adrenalin by the intracardiac method during Adams-Stokes attack,

barium chloride, in doses of 30 mgm. four times daily for seven days, was given, with the object of preventing the recurrence of the attacks. The patient died two months after the cessation of the drug. Herrmann and Ashman[3] have described two cases of Adams-Stokes syndrome treated with barium chloride, one of a severe grade of partial heart-block and the other of complete block. Barium chloride was exhibited in large dosage, without any toxic effect. One patient received a total of 10.98 gm. in 67 days, after which the dosage was reduced to 50 mgm. daily. The other patient received 840 mgm. in 8½ days. In both cases there was a remarkable improvement, the pulse-rate in one increasing from 26-34 to 72, and in the other case from 34-38 to 50-70. In the second case, however, the administration of antispecific treatment (mercury and iodide) should be taken into account. Herrmann and Ashman[3] are of opinion that in their cases barium chloride certainly increased the irritability of the idioventricular pacemaker. They are further of the opinion that, in order to maintain a minimum concentration of the drug, it should be taken continuously in small doses; indeed, they believe that its intermittent use may even be dangerous.

Heard, Marshall and Adams[47] have published a case of Adams-Stokes syndrome in a patient showing varying degrees of partial heart-block—a mere increase in the P-R interval, 2:1, and 3:1 alternating. A total quantity of 5 gm. of barium chloride was administered during a period of three months. The result was not only not beneficial, but also the attacks continued with gradually increasing frequency. B. T. Parsons-Smith[48] has reported a case of complete auriculoventricular block, with a ventricular rate of 30 per minute, subject to Adams-Stokes syndrome. The exhibition of adrenalin at first prevented the occurrence of the attacks. Later, owing to their recurrence, barium chloride, ½ gr. doses twice daily, was given. A gradual increase of the ventricular rate was noted, until at the end of four months an electrocardiogram showed normal rhythm, with a rate of 72. Still later, however, in spite of the continued administration of the drug, reversion to complete heart-block occurred, but without Adams-Stokes attacks, and there was also an improvement in the exercise tolerance. Strauss and Meyer[4] have recently published a case of transient complete heart-block with Adams-Stokes syndrome, in which the employment of a daily dosage of 120 mgm. of barium chloride was followed by an almost entire cessation of the attacks and, although the dosage was relatively large, without any toxic symptoms. It is interesting to note that whereas the majority of cases of transient complete heart-block (Carter and Dieuaide[49]) pass into permanent complete heart-block, it did not occur in this case. Strauss and Meyer[4] further noted that, while pressure on the vagi produced complete heart-block before the administration of the drug, this did not occur during its administration.

We will now describe two cases which were admitted to the National Hospital for Diseases of the Heart, London, England, under the care of one of us (F. W. P.).

CASE REPORTS

CASE 1.—Mr. M., admitted to hospital, July 23, 1926. The following history was obtained: Age, 69 years; widower; married twice; had seven children; five living; two died in infancy. A clerk. Smokes 6-7 oz. tobacco per week. A teetotaller. Ten years ago he had "rheumatism," in the joints of arms and legs, disabling him, lasting about a year. No history of specific disease. About ten years ago, in his usual health, on a very hot day while walking in the sun, having had no premonitory symptoms, he suddenly fell to the ground unconscious, the loss of consciousness lasting only a few seconds. Did not bite tongue, nor pass urine or feces. After recovering consciousness, he continued his work. Many weeks later, a second similar attack, and recurrence of such about once a month for six years, then free for three years. About a year before admission to hospital, attacks began again. For first two or three weeks, two or three attacks per diem, occurring at intervals varying from five minutes to some hours. The attacks gradually increased in frequency, until they reached forty or more per diem, and sometimes patient was continually passing in and out of attacks. Has been in bed for four or five months. No diminution of frequency of attacks while in bed. Patient said that he occasionally felt the heart "stop," this immediately followed by feeling that he "is going." Patient's son-in-law, a qualified masseur, stated as follows: "At the commencement of attacks there is a definite, but transient, flush, followed by pallor of the cheeks, and cyanosis of the lips and nose. Period of loss of consciousness lasts up to four minutes." He sometimes thought the patient was dead. "There are sometimes convulsions, depending upon the length of time of unconsciousness. They affect the face, less frequently the arms, and still less frequently the whole body. They are sometimes accompanied by deviation of the eyes and of the mouth to either side. Stertorous breathing during severe attacks. No vomiting. Pulse rate between the attacks is 20-30 per min. At the commencement of attack, it falls to as low as 11 per minute, this invariably followed by a long pause, varying from 30 seconds up to three minutes. Pulse is very often palpable before return of consciousness, but sometimes both coincide." On one day about June 15 for about 12 hours, patient was continually passing in and out of attacks. Patient thought that he had sometimes been able to prevent an attack from coming on by taking an unusually long breath. Excepting during the three years that he was free from attacks, he suffered from shortness of breath on exertion. On admission: Pulse regular, unless, as was sometimes the case, extrasystoles were present, the latter sometimes occurring at irregular intervals and at other times after each ventricular beat. On admission the ventricular rate was 26 per minute; afterward it varied from 20-26 per minute, excepting when extrasystoles were present. No evidence of thickening of wall of radial artery, but that of brachial considerably so and rather tortuous. Blood pressure about 160-65 mm. Apex beat in the fifth intercostal space, and its force moderately increased. A rough, harsh systolic murmur over the whole precordium and the vessels of the neck. Physical signs of a moderate degree of emphysema. No nocturnal polyuria. Urine had S.G. of 1.014, contained a faint trace of albumin, but no sugar was present. On screening, left border of heart in nipple line, right border 2 inches to the right of the sternum, and transverse measurement of organ 6¾ inches—thus, considering age and build, much enlarged. The aortic shadow was diminished in translucency; its transverse measurement was increased, being 3¼ inches, and left margin was

curved. An electrocardiogram taken July 27 indicated marked left-sided preponderance and complete auriculoventricular block, and there was inversion of the T-wave in all leads, very slight splintering of the R-deflections, and an extrasystole, arising in the apical or left portion of the ventricle, after each ventricular complex of normal form in the second and third leads. Wassermann reaction negative. Subsequent progress: August 7, numerous attacks daily since admission. Pulse rate was counted during one of them. There was an absence of pulse for 10-15 seconds, and after an attack the rate was 12 per minute. August 12, numerous attacks daily still continued; 10 minims of 1/1000 solution adrenalin hydrochloride hypodermically during an attack, with no apparent effect. August 13, very numerous attacks, there sometimes being only three or four ventricular contractions between two attacks. During an attack the patient became pale, then after from five to ten seconds (timed) head dropped back, face became cyanosed, eyes deviated to the right, and clonic spasms of facial muscles commenced. Spasms extended to muscles of neck, and in the longer syncopal attacks they became general. With onset of clonic spasms, breathing became stertorous. During some attacks no ventricular contractions for 35 seconds. With the first ventricular contraction consciousness was rapidly regained and face became flushed. One attack lasted five minutes. On one occasion the resident medical officer pronounced patient to be dead and screens were placed round the bed. After attacks had been occurring every few minutes, 15 minims 1/1000 solution adrenalin hypodermically. This was followed immediately by an attack, but patient was free for about an hour afterward. Ventricular rate was 12 a half hour after injection. August 14, numerous attacks during the night and until 9:45 A.M., when 15 minims 1/1000 solution adrenalin were administered. At 12:15 P.M. had had only two subsequent attacks. An unusually long attack at 4 P.M. August 19, numerous attacks, including one long one, 15 minims 1/1000 solution adrenalin together with 1/100 gr. atropine given, with no effect, frequent vomiting. August 20, numerous attacks, including two long ones. One lasted 1 minute and 10 seconds, during which respiration ceased. Strychnine 1/30 gr., at 10:15 A.M., and 15 minims adrenalin at 3:30 P.M. Frequent vomiting. August 22, only four or five attacks, including one or two slight ones. August 25, attacks greatly reduced in number since August 20 until early that morning, since then fairly frequent but short attacks, fifteen minims 1/1000 solution adrenalin. August 26, 15 minims 1/1000 solution adrenalin hypodermically. August 27, 15 minims 1/1000 solution adrenalin hypodermically. September 8, electrocardiogram as before, excepting that extrasystoles in all leads. September 10, patient was continuing to have attacks, but of short duration. September 13, commenced liq. atropine, by the mouth, 1 min. thrice daily. September 24, no attacks for two days until that morning, then numerous minor attacks. September 26, was free from attacks for three days until this day; those of short duration returned. Ventricular rate 20. Jugular pulsations about 80. October 4, still having rather bad attacks. Pulsus bigeminus, ventricular rate being 40 and pulse rate 20 per minute. October 7, atropine suspended; barium chloride, ½ gr., twice daily, commenced. October 8, barium chloride, ½ gr., thrice daily. October 11, no attacks since commencement of barium chloride. October 15, three severe attacks. Ventricular rate 26, excepting when occasional coupling of beats. Barium chloride increased to gr. 1 thrice daily. October 25, no further attacks. Still on barium chloride, gr. 1, thrice daily. Ventricular rate 26, excepting when occasional coupling of beats. October 29, administration of barium chloride stopped. November 2, commenced to get up. November 4, free from attacks. November 5, electrocardiogram as before, but no extrasystoles present. Discharged from hospital November 11. March 4, 1929, patient had been free from attacks since

discharge from hospital, and led a fairly normal life. Ventricular rate 31. Blood pressure 216/74 mm. Electrocardiogram as on last occasion.

It will be noted that this was a case of Adams-Stokes syndrome of very exceptional severity occurring in auriculoventricular block in which complete success followed the administration of barium chloride after other measures had failed. As far as our knowledge of the literature on the subject goes, the case is a unique one.

CASE 2.—Mrs. M., admitted to hospital February 22, 1928. The following history was obtained: Age 65 years. Seven children, alive and well. Patient had influenza and was confined to bed for over a week in 1923; and was again confined to bed for about a fortnight in September, 1926. No other previous illnesses. Wind and strength up to normal until after second attack of influenza, since then increasing shortness of breath, palpitation and exhaustion on exertion. In the summer of 1927, while in a cinema, suddenly seized with "giddiness," immediately followed by loss of vision, i.e., "things went black," and a sensation of "heat" from the lower part of the back to the top of the head, immediately followed by momentary loss of consciousness, which patient described as "losing herself." Three or four more attacks, less severe, later in the day. Since then patient had been subject to attacks, consisting of the same symptoms. They lasted only for a few seconds, and were followed by a sense of exhaustion. She had never fallen during an attack but supported herself by laying hold of the nearest object. The attacks came on without apparent cause. Since the first attack patient had also been subject to giddiness, not followed by other symptoms. Just before December, medical attendant remarked to her that she had a "remarkably slow pulse." The attacks increased in frequency; and for some hours on one day during the first week in December they were so frequent as to be separated by intervals of only a few moments' duration, on account of which patient stayed in bed for a fortnight, at the end of which time they had diminished to two or three per diem. A recurrence of frequent attacks on January 1, 1928. On February 16, patient came in a motor car to the out-patient department of the hospital. While in the waiting room, she had at least seven attacks. She was admitted as an in-patient on February 22. On admission: Pulse was regular. Ventricular rate 36 per minute. No evidence of thickening of walls of radial or brachial arteries. Blood pressure 240/84 mm. Force of apex beat rather considerably increased. A rather loud systolic murmur and second sound rather considerably accentuated in the aortic area. A moderate systolic murmur at the apex propagated from the aortic area, becoming louder on lying down. No nocturnal polyuria, and nil abnormal on examination of urine. On screening, left border of heart ¼ inch outside midclavicular line, right border 1 inch to the right of the sternum, and transverse measurement 5¾ inches—thus, considering age and build, moderately enlarged. The aortic shadow is rather wide, measuring 2¼ inches. An electrocardiogram shows left-sided preponderance, inversion of T in Leads II and III, and complete auriculoventricular block. Wassermann reaction negative. Subsequent progress: At first 20-25 attacks per diem, but by February 28 they had diminished in frequency. On March 5, barium chloride, in pill form, ½ gr. twice daily, administered for seven days; then dosage was increased to 1 gr. thrice daily. No diminution in frequency of attacks. March 17, 1/100 gr. atropine hypodermically, with no effect. March 20, attacks as before. Ventricular rate 40 per minute. An electrocardiogram as before. April 14, atropine, 1/50 gr., hypodermically. Ventricular rate 36 per minute at time of injection, 36 fifteen minutes later, and 34 fifteen minutes later. April 20, attacks

continued without change. April 27, electrocardiogram as before. April 28, no diminution in frequency or severity of attacks. Was still on barium chloride, 1 gr., thrice daily. Commenced 5 minims 1/1000 solution adrenalin hypodermically thrice daily, which injections were continued. No attack since first injection of adrenalin. May 8, was very much better. No further attacks. Blood pressure 250/100 mm. Size of heart the same. May 11, electrocardiogram showed 2:1 auriculoventricular block instead of complete heart-block. May 21, patient up for half an hour; increased on May 23 to one hour. May 26, patient was still on barium chloride, in same dosage. Adrenalin hypodermically reduced to twice daily. May 29, felt much better. Still no further attacks. Ventricular rate 40 per minute. Blood pressure 230/90 mm. Barium chloride by the mouth and adrenalin hypodermically, both in same dosage, were continued. June 2, adrenalin hypodermically reduced to once daily. June 5, recurrence of attacks. Adrenalin hypodermically increased to twice daily. June 21, no recurrence of attack. Dosage of adrenalin hypodermically changed to 10 minims once daily. Patient was discharged June 26, still having 1 gr. of barium chloride thrice daily by the mouth, and 10 minims of adrenalin hypodermically once daily. January 28, 1929, the treatment by barium chloride by the mouth and adrenalin hypodermically was continued, but some time during Christmas week the daily dose of adrenalin was reduced from 10 to 8 minims. Patient's medical attendant recently taught her to give the hypodermic herself. She usually did this about midday, failing which, she postponed it until bedtime, in which event she did not feel nearly so well. She felt better than she had for two years. On examination: Pulse regular. Ventricular rate 48 per minute. Blood pressure 278/92 mm. On screening, heart as before. An electrocardiogram revealed 2:1 auriculoventricular block instead of complete auriculoventricular block.

It will be observed that this was a case of Adams-Stokes syndrome due to complete auriculoventricular block in which a satisfactory result followed the administration of barium chloride by mouth together with adrenalin hypodermically, and in which the use of barium chloride alone was quite ineffective. It is worthy of note that an electrocardiogram taken ten days after the commencement of the administration of adrenalin hypodermically, in addition to barium chloride by mouth, revealed 2:1 auriculoventricular block, instead of complete auriculoventricular block. An electrocardiogram taken on January 28, 1929, showed that the former was still present.

It would appear, therefore, from a study of the foregoing cases, that the exhibition of barium chloride, administered by the mouth, failing which, barium chloride together with adrenalin, the latter given either hypodermically or intramuscularly, is indicated for the prevention of the recurrence of Adams-Stokes syndrome due to auriculoventricular block. We would recommend the following: That barium chloride be administered, at first in doses of ½ gr. thrice daily. This dosage should, if necessary, be cautiously increased—stopping short of toxic symptoms—to 1 gr. thrice daily. With regard to adrenalin, 0.5 c.c. to 1 c.c. of $\frac{1}{1000}$ solution thrice daily until after the attacks have ceased for some time. The dosage of adrenalin should then be gradually diminished until the drug is omitted altogether. Still later, the dosage

of barium should be gradually reduced to the minimal dose found necessary to prevent the recurrence of the attacks.

SUMMARY

A. The pathogenesis of Adams-Stokes syndrome due to auriculoventricular block is described.

B. The primary aim and the rationale appertaining to any therapeutic measure is discussed. These are shown to be an increase in the ventricular rate, brought about in one or more of the following ways: (1) the resolution of the lesion, as, for example, in gummatous infiltration and acute inflammatory changes; (2) the counteraction of any possible vagal overactivity; (3) the increase directly of stimulus production, of excitability and of contractility of the heart muscle.

C. The rationale and the comparative value of various therapeutic measures are discussed.

Antisyphilitic treatment is indicated in Adams-Stokes syndrome due to auriculoventricular block when this is the result of gummatous infiltration.

Potassium iodide may even aggravate the complaint when the cause is other than syphilis.

Thyroid appears to be sometimes of value and may even be completely effective.

Atropine, administered between the attacks, in order to prevent their recurrence, is indicated in cases of partial heart-block in which there is vagal overactivity.

Digitalis is contraindicated in partial heart-block. It may be of value in complete heart-block.

Caffeine and theobromine are of no clinical value.

Of reported cases, the nitrites were found to be only of doubtful value in one case.

Adrenalin is of value in the great majority of cases. It is not often effective in preventing the recurrence of the attacks. When employed for this purpose, it may be administered either subcutaneously or intramuscularly. It is, however, the only potent therapeutic measure during an attack. When employed for this purpose, intracardiac injection is necessary, except in the rare cases in which the attacks are due to a merely temporary increase in the grade of an existing partial heart-block, in which event it may be given either hypodermically or intramuscularly.

Further investigation of ephedrin, administered by mouth, is advisable.

Barium chloride, given by mouth, should invariably be tried for the prevention of the recurrence of the attacks in cases of Adams-Stokes syndrome due to auriculoventricular block. If ineffective alone, the drug should be employed with adrenalin, the latter administered either hypodermically or intramuscularly.

REFERENCES

1. Lewis, T.: Mechanism and Graphic Registration of the Heart Beat, London, 1925, third edition, p. 421, Shaw & Sons.
2. Cohn, A. E., Holmes, G. M., and Lewis, T.: Heart **2**: 241, 1910-1911.
3. Herrmann, G. R., and Ashman, R.: Am. Heart J. **1**: 269, 1926.
4. Strauss, S., and Meyer, J.: Am. Heart J. **3**: 328, 1928.
5. Blackford, J. M., and Willius, F. A.: Am. J. Med. Sc. **154**: 585, 1917.
6. Aub, J. C., and Stern, N. S.: Arch. Int. Med. **21**: 130, 1918.
7. Willius, F. A.: Canad. M. J. **14**: 1072, 1924.
8. Drake, E. H.: Am. Heart J. **3**: 560, 1928.
9. Erlanger, J., and Hirschfelder, A. D.: Am. J. Physiol., B. **15**: 153, 1906.
10. Fredericq, L.: Arch. Int. de Physiol. **11**: 405, 1912.
11. Kahn, R. H.: Arch. f. d. ges. Physiol. **140**: 627, 1912.
12. Van Egmond, A. A. J.: Arch. f. d. ges. Physiol. **154**: 39, 1913.
13. Hirschfelder, A. D.: Diseases of Heart and Aorta, Philadelphia, 1918, third edition, p. 585, Lippincott.
14. Cohn, A. E., and Levine, S. A.: Arch. Int. Med. **36**: 1, 1925.
15. Von Tabora, D.: Ztschr. f. exper. Pathol. u. Therap. **3**: 499, 1906.
16. Erlanger, J.: Arch. f. d. ges. Physiol. **127**: 77, 1909.
17. Rothberger, C. J., and Winterberg, H.: Arch. f. d. ges. Physiol. **150**: 217, 1913.
18. Meek, W. J., and Eyster, J. A. E.: Am. J. Physiol. **38**: 62, 1915.
19. Hoskins and Lovette: J. A. M. A. **63**: 316, 1914.
20. Korns, H. M., and Christie, C. D.: J. A. M. A. **79**: 1606, 1922.
21. Cushny, A. R.: Textbook of Pharmacology and Therapeutics, 1928, ninth edition, p. 387, J. A. Churchill.
22. Hering, H. E.: Arch. f. d. ges. Physiol. **108**: 281, 1905.
23. Cullis, W. E., and Tribe, E. M.: J. Physiol. **46**: 141, 1913.
24. Routier, D.: C. R. Soc. de Biol. **78**: 375, 1915.
25. Hardoy, P. J., and Houssay, B. A.: J. de Physiol. et de Pathol. génér. **17**: 605, 1917-18.
26. Clerc, A., and Pezzi, G.: Journ. de physiol. et de pathol. gén. **18**: 965, 1919-20.
27. Kahn, R. H.: Arch. f. d. ges. Physiol. **129**: 379, 1909.
28. Danielopolu, D., and Danulescu, V.: C. R. Soc. de Biol. **79**: 861, 1916.
29. Ibid: p. 105.
30. Strisower, R.: Wien. klin. Wchnschr. **33**: 269, 1920.
31. Parkinson, John, and Bain, C. W. Curtis: Lancet **2**: 311, 1924.
32. Arrilaga: Abstr. Arch. des mal. du coeur **13**: 370, 1920.
33. Lutembacher, R.: Arch. des mal. du coeur **13**: 345, 1920.
34. Phear, Arthur G., and Parkinson, John: Lancet **1**: 933, 1922.
35. Feil, Harold: J. A. M. A. **80**: 26, 1923.
36. Miller, T. Grier: Am. J. Med. Sc. **170**: 157, 1925.
37. Stecher, R. M.: Am. Heart J. **3**: 567, 1928.
38. Junkmann, Karl: Arch. f. exper. Path. u. Pharmakol. **108**: 149, 1925.
39. Boehm, von: Arch. f. exper. Path. u. Pharmakol. **3**: 216, 1875.
40. Ringer, S.: Brit. M. J. **2**: 265, 1883.
41. Brodie and Dixon: J. Physiol. **30**: 476, 1904.
42. Magnus, D.: Arch. f. d. ges. Physiol. **108**: 1, 1905.
43. Rothberger, C. J., and Winterberg, H.: Arch. f. d. ges. Physiol. **142**: 461, 1911.
44. Wilson, F. N., and Herrmann, G. R.: Arch. Int. Med. **31**: 923, 1923.
45. Levine, S. A.: Boston M. & S. J. **195**: 1147, 1926.
46. Levine, S. A., and Matton, M.: Heart **12**: 271, 1926.
47. Heard, Marshall, and Adams: Am. Heart J. **2**: 562, 1927.
48. Parsons-Smith, B. T.: Proc. Roy. Soc. Med. (Clinical Section) **20**: 34, 1927.
49. Carter, E. P., and Dieuaide, F. R.: Bull. Johns Hopkins Hosp. **34**: 401, 1923.

CONGENITAL HEART DISEASE; EXTREME CONGENITAL PULMONARY STENOSIS (TETRALOGY OF FALLOT); COLLATERAL PULMONARY CIRCULATION; MASSIVE RIGHT-SIDED VEGETATIVE ENDOCARDITIS*

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THE comparative rarity of congenital cardiac defects and the need for their further detailed clinico-pathological study seems to justify the reporting of all instructive cases. The type here presented, often called the "tetralogy of Fallot," is that which is met with most frequently by the practitioner. It is characterized by four anatomical changes, namely, (1) pulmonary stenosis, (2) defect in the interventricular septum, (3) dextraposition of the aorta, and (4) hypertrophy of the right ventricle. Characteristically, cyanosis, clubbing and polycythemia are present in varying degrees according to the extent of the irregularities in the circulation which interferes with oxygenation of the blood.

Clinically, the condition is important, not only because of its frequency, but also because, of the more serious cardiac anomalies, it permits a relatively long duration of life; and although the prognosis is always more or less grave, according to the extent of the lesion, something may be accomplished in treatment by regulation of mode of life and other measures. White and Sprague[1] have recently reported the interesting case of Gilbert, a noted American musician and composer who attained the age of 59 years, having suffered all his life from a marked degree of this type of disease. Great care to avoid fatigue and to guard against infection doubtless contributed much to prolong his life.

HISTORICAL

Sandifort in 1777 first described the condition which later became known as the tetralogy of Fallot. As long ago as 1814, Farre stated that it was the commonest malformation of the heart. The first extensive study, however, seems to be that of Peacock[2] who in 1866 was able to collect 60 published references to this anomaly. Fallot[3] in 1888 brought together clinical and pathological findings in a very clear manner, and since that time his name has been associated with this particular type of anomaly. In the more recent literature Dr. Maud Abbott's classical monograph[4] in the 1927 edition of Osler's Modern Medicine

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reviews completely our present knowledge of congenital heart disease. Her work is based upon the study of 850 defects with autopsy findings. A localized defect at the base of the interventricular septum occurred in 240 cases. Of these, 54 were classified as the primary lesion and 186 complicated other anomalies. Of these 186 cases of defect at the base, 95 were in cases of pulmonary stenosis or atresia, among which dextraposition of the aorta occurs 62 times. In Abbott's series the occurrence in the same heart of a defect at the base of the interventricular septum, pulmonary stenosis or hypoplasia of the developmental type, and dextraposition of the aorta makes up the commonest of all combinations in congenital heart disease. Hypertrophy of the right ventricle is always present and so constitutes the fourth pathological element in the complex.

PATHOGENESIS

Many earlier writers sought to explain the causal connection suggested by the association of these anomalies. The theories of their etiology and pathogenesis are too involved for discussion here, but a few points may be mentioned, however. All cardiac anomalies occur either as the result of arrest of growth at an early stage, or by fetal disease in the more fully developed heart. There is much evidence to point to the former as the etiological factor in most cases, including the condition described here. Those resulting from endocarditis in later fetal life are thought to be confined to a small group in which the stenosis is strictly limited to the valves, and with no associated septal defect. In cases of developmental origin the arrest must have occurred some time before the end of the second month of gestation at which time the heart is complete.

The explanation by Keith,[5] brought out over twenty years ago, is now generally accepted. He concluded that in the majority of the cases the stenosis is primary in the conus and is the result of an arrest of development at a stage when there existed in the heart a fourth primitive chamber, the bulbus cordis. Tracing the evolutionary changes from the fish and reptiles, Keith described how in the mammalian heart the bulbus cordis has become separated from the left ventricle and aorta and is completely incorporated in the right ventricle as the infundibulum of that chamber. This occurs during the first month of gestation. As he says, "The submergence of the bulbus constitutes a critical phase in the developmental metamorphosis of the heart, and it is during this time that malformations are apt to occur," so that whatever agent may be at work in producing these malformations must exert its effect at this early stage of development.

Fallot's tetralogy centers around the pulmonary stenosis which is the essential part of the anomaly, etiologically and clinically. Cyanosis is such a constant feature that morbus caeruleus and pulmonary stenosis

have been considered almost synonymous terms. The presence of an interventricular septal defect indicates that early stage at which the stenosis took place. The clinical aspects vary somewhat with the situation and extent of the deformity. These may profitably be considered in connection with the present case, which exhibited all typical symptoms and signs.

CASE REPORT

E. M., a female, aged 16 years, was admitted to the University of Michigan Hospital, December 10, 1928, complaining of "heart trouble."

Present Illness.—Cyanosis had been present since birth. As a child the patient was always backward. She did not walk until 3 years of age. At the age of 6, following whooping cough, the cyanosis became very prominent. She had always complained of cough and pain in the precordium on exertion. Cyanosis was much accentuated with increased muscular activity. Even after walking a block or so she was compelled to stop and rest. In spite of this the patient had always been

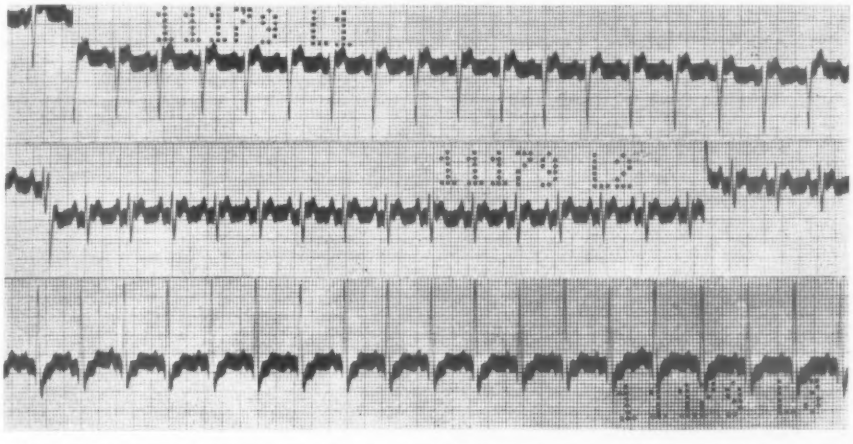

Fig. 1.—Electrocardiograph tracing showing marked right ventricular preponderance.

up and about. In the summer prior to admission she had used roller skates, but these were finally discarded because she had swelling of the ankles. About a month before entrance to hospital she had three teeth pulled. The gums continued to bleed. After two days she had a temperature of 102° F. A week later the temperature was still elevated, and the patient was confined to her bed. During the two weeks preceding entrance, gross blood was noted in the urine. She developed severe epigastric and precordial pain. She was tender all over the body and was troubled with an occasional dry cough. Shortness of breath was not prominent, but there was a deepening of the cyanosis.

Past History.—The patient was the last child of a family of eight; there were three sisters and four brothers living and well. Her mother was about 47 and her father 56 when she was born. The patient had smallpox, measles and whooping cough and had also been subject to occasional sore throats. She had always been constipated. She had grown to normal height but was always thin. Menses began at the age of 14 years and had always been irregular. The patient had been considered to some degree mentally deficient.

Family History.—Father died of heart disease at the age of 69. Mother died of Bright's disease at 60. As far as could be ascertained there was no history

of congenital heart disease in the family and none of her brothers and sisters had obvious abnormalities.

Physical Examination.—The patient was a poorly nourished, adolescent female, lying flat in bed with moderate dyspnea and marked cyanosis. The nose, lips, malar prominences and hands appeared purple. The gums were bleeding. The tongue gave the impression of dehydration. The tonsils were enlarged. The chest showed a bulging over the precordium. The sternocostal junctions were prominent. There was a marked scoliosis to the left in the dorsal region. A pulsation was noted in the third and fourth interspaces on the left. There was a questionable precordial thrill. The heart was enlarged to percussion, the borders being 11 cm. to the left in the fourth interspace, and 6 cm. to the right. The rhythm was regular, the rate 120. A loud systolic murmur was best heard in the

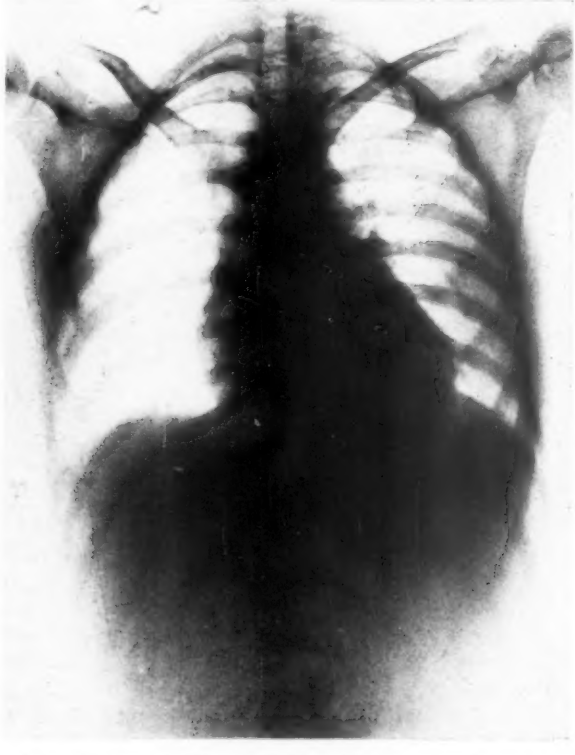

Fig. 2.—X-ray plate of chest showing large heart, cervical ribs and thoracic scoliosis.

second, third and fourth interspaces just to the left of the sternum. No diastolic murmur could be detected. The pulmonary second sound was moderately loud. The lungs showed only diminished breath sounds and a few râles at the left base. The liver was palpable just below the costal border. Edema was absent, but there was marked clubbing of the fingers and toes.

Laboratory Findings.—The Kahn test was negative. Urine showed a specific gravity of 1.020, with albumin and many granular and hyaline casts. Gross blood was present on one occasion. Blood examination showed: hemoglobin 100 per cent; red blood cells, 7,450,000, and the white blood count 19,500; differential count, polymorphonuclears 68, lymphocytes 31, eosinophiles 1. The blood culture was negative. Electrocardiograph tracings showed marked right ventricular preponder-

ance and sinus tachycardia (see Fig. 1). X-ray examination of the chest showed cardiac enlargement, scoliosis to the left, and bilateral cervical rib (see Fig. 2).

Course in Hospital.—At entrance the temperature was 103° F. and was continually above 100° and went as high as 105°. The pulse was rapid and the respirations at times were Cheyne-Stokes in type. The cyanosis decreased somewhat with absolute rest, but the weakness increased and the mental state became clouded. Oxygen was given but with no marked results. On December 17, 1928, a week after admission, the patient died.

Clinical Diagnosis.—Congenital heart disease, probably pulmonary stenosis with interventricular septal defect and a superimposed infection in the form of septicemia or bacterial endocarditis. Scoliosis. Bilateral cervical rib.

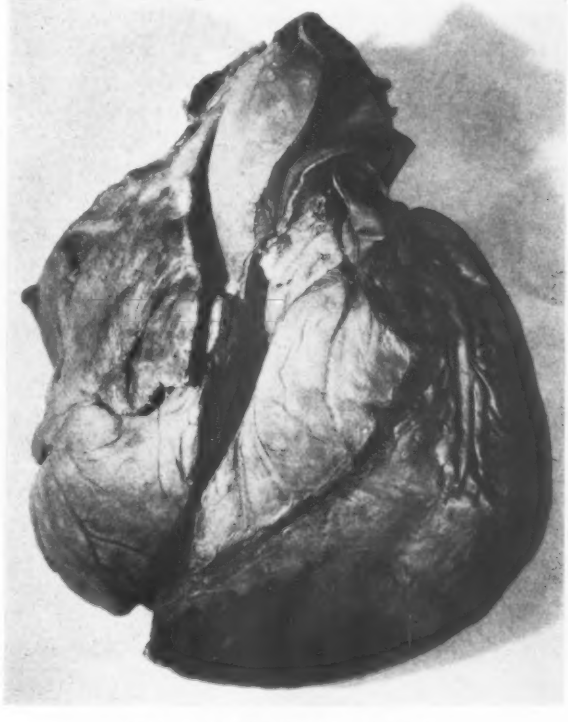

Fig. 3.—Anterior view of heart.

AUTOPSY

The summary of significant gross findings, apart from the heart, is as follows: Body was that of a poorly nourished, adolescent female, 154 cm. in length, showing the features of the asthenic type and having the appearance of an inferior degenerative constitution. There was a distinct brachygnathia. There was a marked thoracic scoliosis. There was very marked clubbing of all fingers and toes and a marked generalized cyanosis of the skin, with also a faint icteroid tinge. The spinal cord showed congestion and edema. There was an asymmetry of the calvarium with a depressed area measuring 6 cm. in diameter in the part of the cranium occupied by the posterior fontanel in the infant. This was evidently a congenital defect. The fifth and sixth costal interspaces were widened at their union with the sternum. There were bilateral cervical ribs. The one on

the right articulated at its tip with the first rib. The left had a free tip. The twelfth rib on either side was very short and rudimentary. The cardiac apex was in the fourth intercostal space halfway between the midclavicular and anterior axillary lines. The right border measured 6 cm. to the right of the midsternal line. The pericardium was apparently normal. (The heart will be described in detail below.) The lungs felt leathery. They were a dark purplish color from the extreme congestion but showed no evidence of pneumonia or tuberculosis. There were no pleural adhesions. The spleen was large, weighing 390 grams; the liver 1770 grams. Both showed evidences of chronic passive congestion. The kidneys were congested and showed swelling and a few small fresh anemic infarctions.

Microscopic examination showed a marked congestion of all tissues. The liver and spleen showed chronic passive congestion. In the lungs there was extreme congestion and edema, on a chronic passive congestion, and fibrosis. The renal glomeruli were usually large. One of the clubbed toes was examined microscopically and showed chronic productive periosteitis toward the tip with thickening of the blood vessels.

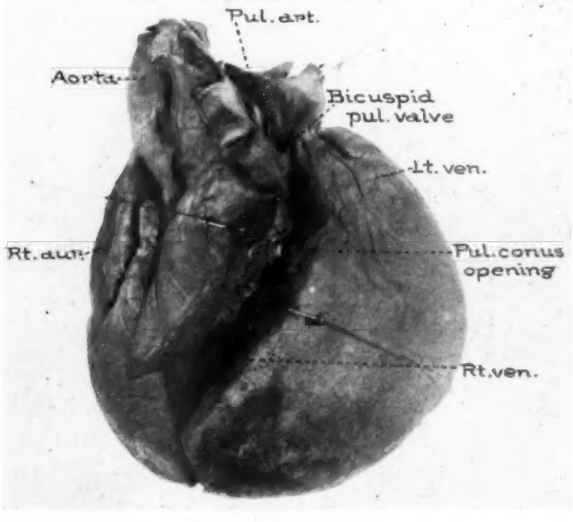

Fig. 4.—Anterior view of heart with pulmonary tract spread open.

DETAILED DESCRIPTION OF HEART

The heart weighed 290 grams. It is of a peculiar shape, being broad transversely in comparison with longitudinal measurements. The apex is broad and flat, lacking the conical shape as seen in the normal heart. Externally there is no division visible between right and left ventricles (see Fig. 3). The great vessels arise in the normal relationship, except that the aorta appears to arise from both ventricles, while the pulmonary artery is very small, thin walled, and arises anteriorly and to the left of the aorta. The transverse measurement across the ventricles at the widest point is 11 cm. The length from the base of the aorta to the apex is 9 cm., and from the superior vena caval opening in the right auricle to the apex 10 cm. The anteroposterior thickness of the ventricles is 6 cm.

The epicardium is smooth and shining. There is a moderate amount of subepicardial fat. The superior and inferior venae cavae appear normal in size and open into the right auricle in normal relationship. This cavity is moderately dilated. The muscular wall is slightly thicker than normal. The musculi pectinati

are prominent. One of these is attached only at its extremities and stretches across the opening of the superior vena cava a distance of 2 cm. Attached to this round muscular band, which is 2 mm. in thickness, there are several thread-like structures traversing the cavity with thin attachments on the superior wall of the auricle (Chiari's network).

The valve of the inferior vena cava persists but is not prominent. The fossa ovalis is in the normal position. From its superior aspect an elliptical inter-auricular opening persists. This patent foramen ovale, valvular in form, will admit a probe 1 cm. in diameter. The coronary sinus, protected by its valve, opens in its normal relationship just below the limbus of the fossa ovalis.

The pars membranacea septi as viewed from the right auricle, is seen to lie in its normal position "at the base of the medial cusp of the tricuspid valve just

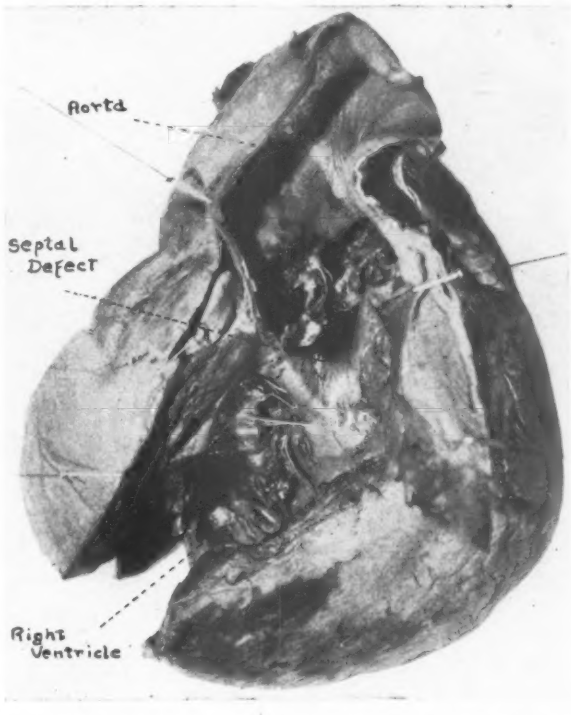

Fig. 5.—Right ventricle opened showing right-lying aorta and interventricular septal defect. Note vegetations on aortic cusps.

posterior to the angle between it and the infundibular cusp, half in the auricle and half in the ventricle" (Abbott).

The tricuspid orifice is directed downward, forward, and to the left. The valve cusps are almost completely destroyed and replaced by great masses of vegetations measuring as much as 15 to 17 mm. in thickness. This luxuriant growth not only invades the valve but also extends well into the musculature of the walls and into the papillary muscles (see Fig. 6).

The musculature of the right ventricle is greatly hypertrophied, averaging 16 mm. in thickness. The right ventricle composes most of the anterior part of the heart. The cavity appears dilated but in form is somewhat flattened and elongated. The cavity is partially divided into two parts by a thick muscular projection running from the anterior part of the interventricular septum, beginning at a

point 2.5 cm. from the apex of the heart, backward, and to the right for a distance of 4.5 cm.; thence it curves forward and downward toward the right to the anterior wall, to be lost in the musculature of the ventricle. This division produces a semilunar orifice about 3 cm. in length and about 1 cm. at its widest point demarcating the conus above from the remainder of the right ventricular cavity below.

Superior to the upper part of this muscular cushion there is a defect in the interventricular septum which admits the index finger. The septal defect, therefore, appears to open into the conus and not into the sinus of the ventricle. The superoposterior part of the conus opens into the aorta. The left inferior part of the conus leads into a small funnel-shaped recess surrounded by thick muscular walls. This latter recess (which, as will be explained later, would appear to represent the lower bulbar orifice) measures 3 cm. below the round margin of the defect in the interventricular septum. This shallow pocket leads immediately into a narrow canal which courses through the thick muscular wall a distance of 6

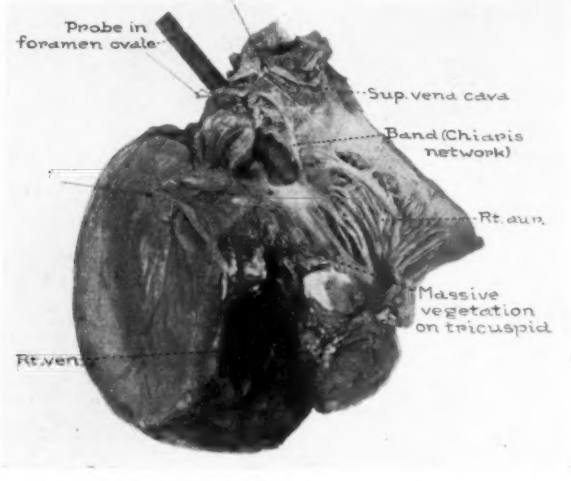

Fig. 6.—Right ventricle and right auricle opened.

mm., thence opening into a larger, thin walled cavity. The channel will just admit a round probe measuring about 3 mm. in diameter. The endocardial lining is thickened but smooth except at its distal portion where there are a few pinhead-sized vegetations projecting from the free surface into the larger cavity. Three cm. above this narrow orifice there are two cusps facing right and left, guarding the pulmonary orifice. These valve cusps are very thin and appear like the valves of a vein. The left cusp is one-third wider than the right. They are free of vegetations (see Fig. 4). The pulmonary artery widens out above these and is situated to the left of the aorta. At its widest portion it measures 3.5 cm. in circumference. The wall appears as delicate as that of the superior vena cava. The ductus arteriosus is completely obliterated. The cavity below the rudimentary bivalvular orifice is conical in form and will just admit the tip of the little finger.

The aorta, as stated above, is continuous with the superior portion of the conus of the right ventricle (see Fig. 5). It rides directly over the interventricular septal defect so that the communication with the right ventricle is about equal to that with the left. The margin of the defect is broad, smooth and shows no sclerosis of the endocardium nor any vegetations. The aortic valves, 2 posterior and 1 anterior, are large. There are fresh vegetations, 5 mm. thick in places,

attached to the ventricular surfaces of the two posterior cusps only, their free margins and their attachments being smooth. The sinuses of Valsalva are capacious. The coronaries arise in the normal manner from behind the left posterior and the anterior cusps.

The condition of "Rechtslage" or right-lying aorta, is made plain by the following anatomical proof.[5] In the normal heart the pars membranacea septi lies at the base of the right posterior aortic cusp and between it and the anterior cusp. In this case, however, it is situated between the bases of the right and left posterior cusps. Thus, the right posterior cusp lies in front of instead of behind, the pars membranacea (see Fig. 6).

The first portion of the aorta measures 6 cm. in circumference. The wall is of normal thickness and the intima is smooth.

The left auricle is small, and its wall is thin; the pulmonary veins open normally into it, three to the right and two to the left. The mitral valve appears normal. The anterior cusp measures 5 cm. and the posterior 3 cm. The margins are not thickened and are free from vegetations.

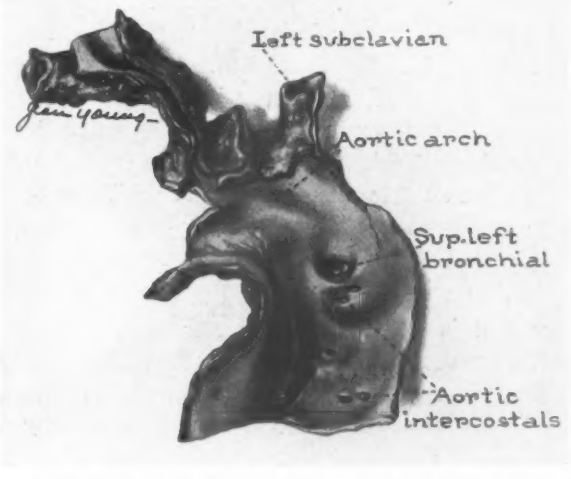

Fig. 7.—Drawing of dissection of upper thoracic aorta showing very large superior left bronchial artery.

The left ventricle makes up less than half the heart in bulk. The cavity is moderately dilated. The wall averages 12 mm. in thickness. The endocardium is smooth and shining. The interventricular septal defect measures 6 cm. from the apex of the cavity. The channel leading from the left ventricle toward the aorta at the level of the septal defect is about the same size as that from the right ventricle. At the rounded borders of the defect the septum measures 11 mm. in thickness (see Fig. 6).

The coronary vessels appear normal as to their size and distribution. The aortic end of the ductus arteriosus is entirely obliterated, and there is no coarctation at any point in the aorta. The branches of the pulmonary artery, though small and vein-like, divide and are distributed to the lungs in a normal manner.

The full collateral circulation to the lung was not worked out at time of autopsy. Later dissection, however, indicated that this was mainly or entirely from the bronchial arteries. Examination of the superior left bronchial arising from the aorta shows it to be from four to five times the normal diameter (see Fig. 7).

Microscopic examination of the heart showed diffuse fibrinopurulent endocarditis and myocarditis with numerous colonies of cocci. There was ulceration of the wall. The heart muscle showed cloudy swelling, Zenker's necrosis, edema and congestion. There were collections of leucocytes throughout the heart which also showed atrophy and fatty degenerative infiltration.

The bacteriological reports from cultures taken at time of autopsy were as follows. No growth was obtained on culture of the heart's blood after five weeks' incubation. From the vegetations on the tricuspid valves, however, streptococcus viridans was found on culture.

DISCUSSION

Pathological Anatomy.—The most striking finding was the extreme degree of stenosis of the pulmonary conus, which measured only about 3 mm. in diameter (see Fig. 6). The narrowing was so marked that it might almost be classified as an atresia, as, indeed, very similar cases are described by early authorities. In an atresia reported by Weiss and quoted by Abbott[4] "the conus admitted only a pinhead or a fine straw, and was lined by thickened endocardium; above this were two fairly large pulmonary cusps, and the artery itself was comparatively large. There was a small patent foramen ovale, a large defect of the septum at the base and a large thick walled aorta arose from the right ventricle above the defect." His case was evidently very similar to this one.

The condition of the conus and its relation to the rest of the right heart resembles that in Case 3 described by Abbott, Lewis and Beattie.[6] "The conus is as large as, or larger, than normal but is completely aplastic above and is demarcated below from the sinus of the right ventricle by the hypertrophied muscle bands (crista supraventricularis and trabecula septum marginalis) which mark the site of the lower bulbar orifice of the embryonic heart, thus representing the condition described by Keith as "conus a separate chamber." They make the anatomical conclusion that "in pulmonary stenosis or atresia with septal defect the condition of the conus of the right ventricle, whether hypoplastic or not, will depend upon whether the defect in the septum opens into the sinus of the ventricle or into the conus. In the former case the conus will be small and aplastic; in the latter it will be large and thick walled." As already seen from the description the present case appears to follow this rule.

Another anomaly in the heart quite distinct from the tetralogy of Fallot was the presence of an anomalous network in the right auricle (see Fig. 6). This condition was first described on the basis of eleven original cases by Chiari[7] as a delicate fenestrum extending from the Eustachian valve across the cavum of the right atrium. Heuper and Berghoff[8] added two cases and state that in all seventeen cases have been described. Another one, an extensive network, was seen recently by the writer in a case showing no other anomalies. Chiari came to the conclusion that the network is a definite developmental anomaly, the

threads being residues of the valvula venosa dextra and of the septum spurium. Such a condition is not entirely without clinical significance. Although these strands may exist without giving any evidence of their presence, the fine reticulum in the right auricle may supply a possible nidus for thrombotic processes, which may lead to embolism (Abbott).

The vegetations at the site of the tricuspid valve presented a remarkable appearance on account of their great size, measuring as much as fifteen to seventeen mm. in thickness. The cusps were almost entirely destroyed. The process extended to the walls of the ventricle and caused ulceration. There was even a fibrinopurulent myocarditis as well as endocarditis, and microscopic examination showed numerous colonies of cocci in the deeper layers.

Just here some reference should be made to the bacteriological studies in this case. Repeated blood cultures during life were negative. Also cultures of the heart's blood taken at autopsy showed no growth. But cultures taken from the vegetations themselves produced an abundant growth of Streptococcus viridans. In view of the very severe infection and the evidences of septicemia in the heart and elsewhere in the body it seems remarkable that the heart's blood should be sterile. As accurate statistics on conditions such as this are difficult to procure, no conclusion is drawn, but the possibility is suggested that the same factors responsible for the production of such luxuriant vegetations have the effect of inhibiting growth in the blood stream. Most inflammatory processes involving the right heart seem to be due to the pneumococcus or other microorganisms of higher virulence than the Streptococcus viridans.

The extravagantly fungating character of the vegetations in right-sided lesions where there is a septal defect has been noted and studied by Abbott.[9] No satisfactory explanation has been found to explain why such vegetations surpassing anything ever seen in the left heart should occur here. It is of significance, however, that such a condition occurs in the presence of an arteriovenous shunt. From this fact Boldero and Bedford[10] have suggested that the presence of the oxygenated blood which enters through the defect may be the cause of this redundancy. Abbott thinks this commingling may be indirectly responsible, but that a lessened oxygen unsaturation of venous blood would not alone account for it, since we do not see this rate of growth in vegetations in the left heart in which aerated blood continually flows. Working on this hypothesis and noting the situation of the lesions, the present case helps to illustrate the direction of intracardiac flow in the presence of the septal defect. The tricuspid valve was involved most of all. Throughout the latter part of the disease it must have been incompetent to a greater or less degree, so that the mixed blood flowed back over the cusps. The aortic cusps were involved less, and there were only a few minute vegetations attached to the thickened endocardium at the site

of the conus stenosis. The pulmonary cusps and the entire left heart were free.

It is important to note the parts of the heart involved by the endocarditis because here is additional proof that such processes occur in tissues which for various reasons have become predisposed to this type of infection. The influence of wear and tear in producing *locus minoris resistentiae* is undoubtedly great. A second well-recognized factor is the presence of local deformities, upon which also the first factor may depend. The tricuspid valves must have been the sites of unusual stress and strain. In Abbott's series the highest frequency of this infection was on malformed cusps. In this case the pulmonary valve was exempt, doubtless because it never functioned to any great extent. But the thickened endocardium of the conus opening was the seat of vegetations. Next to deformed valves the commonest site is a septal defect. The margins of the defect in this case, however, were clear, probably on account of the fact that they were not sclerotic. An important predisposing factor is the location of a defect in close proximity to valvular endocardium where there is an area of sclerosis. Thus, endocarditis does not occur around defects in the upper part of the interauricular septum or where the entire interventricular septum is absent.

Associated Anomalies.—It has long been known that congenital defects, particularly those classed definitely as due to arrest of growth, are apt to be multiple in the same individual. Anomalies elsewhere occur so frequently in congenital heart disease that this gives strong support to the view that a common cause is responsible for all. In Abbott's series of 850 cases 17 per cent showed associated anomalies. This association is too frequent to be considered accidental.

In the present case it is interesting to note the multiplicity of anomalies apart from those found in the heart. These conditions aside from the mental deficiency were confined to skeletal deformities.

1. Mental deficiency. The patient had always been considered below par in intelligence. Abbott states this to be not infrequent, although intelligence is sometimes even higher than the average, as instance the case of Gilbert, the composer.

2. Inferior degenerative constitution. This refers to the general type, build, facies, etc. The patient was a slender asthenic type with a long, narrow head and distinct brachygnathia.

3. Asymmetry of the calvaria. This was manifested by a depressed area slightly more to the right in the occipitoparietal region. Such an anomaly was noted by Dr. Abbott in her series.

4. Bilateral cervical rib. The one on the right side articulated at its tip with the first rib. The left was free.

5. Partial suppression of twelfth ribs. Both were very short.

6. Scoliosis.

The underlying cause of such arrests and disturbances of growth still remains obscure. It is generally thought that it is not due so much to a hereditary predisposition as to some constitutional disturbance or disease in the maternal tissues or fetal envelopes, that is, in the environment of the developing embryo. It seems of some significance that the patient in this case was the last child of a family of eight, her mother and father being aged 47 and 56 respectively when she was born. Instances such as this of the occurrence of congenital cardiac defects in children of parents who have both reached middle life have been observed before. Abbott notes the striking parallel in Mongolian idiocy which also occurs usually as an "exhaustion product" of elderly parents, and as the last of many pregnancies.*

Pathological Physiology and Clinical Aspects.—As pointed out by Abbott, Fallot's tetralogy supplies the best example of the "immediate and remote effects of a high degree of oxygen-unsaturation persisting throughout many years. It illustrates the combined effect of a permanent venous-arterial shunt of the circulation through the septal communication as a result of the raised pressure in the right ventricle, and of an increased deoxygenation in the systemic capillaries from retardation of the flow there." All the classical features of this morbus caeruleus, cyanosis, clubbing, dyspnea and polycythemia are the expression of deficient aeration of the blood. Most striking of all is the cyanosis which differs from the cyanosis of later stages of acquired heart disease in that it may exist for many years without any signs of cardiac insufficiency.

The exact explanation of the cause of the cyanosis was long a subject of controversy. Early writers attribute it variously to the following: (1) venous stasis; (2) admixture of venous with arterial blood; (3) deficient aeration; (4) dilatation and new formation of capillaries in the lungs; (5) peripheral parts of the body; (6) changes in the blood itself, i.e., polycythemia. Abbott traces the progression of these views up to the light of our present knowledge and shows how each of the theories contained a part but none the whole of the truth. It remained for Lundsgaard and Van Slyke[11] to clarify and explain the condition in their very important monograph. This work has been of great value in distinguishing the essential causative factors from the modifying ones. A discussion of the present view would be too lengthy for the scope of this paper; but to quote Abbott, it may be summarized by saying that the dependence of congenital cyanosis upon deficient

*At the time of writing, a case of a twenty-two months old male child came to autopsy at the University of Michigan Hospital showing an anomalous, distorted right posterior aortic cusp and double right coronary. Associated anomalies were macrencephaly; hydrocephalus, anomalous lobation of both lungs, absence of left temperomandibular joint, anomalous external ear, accessory auricle, anomalous maxillae, and a sacrococcygeal dimple. Of the last three autopsied cases of harelip, two showed cardiac anomalies, one a cor biatrium triloculare and cor biventriculare triloculare. There is now a patient, a female, aged 28 years, under observation in the department of medicine, with a diagnosis of mild pulmonary stenosis who has also an anomaly of the urethra.

oxygenization is now definitely established. According to Warthin,[12] however, Abbott fails to recognize sufficiently the important recent work on capillary morphology and pathology bearing directly upon the question of morbus caeruleus. He cites the work of Redisch and Rösler which presents an entirely new aspect to morbus caeruleus by their findings of a constant capillary dilatation which they consider to be the cause of the affection. The circulation evidently accommodates itself to a certain degree of oxygen-unsaturation, whether brought about by obstruction in the course of the pulmonary artery, by general retardation of flow, or by a mingling of venous with arterial blood; but as soon as deficient oxygenization reaches a certain limit, this becomes insufficient for the needs of the body, and cyanosis results. Thus, in the present case, the patient was always much bluer upon exertion. Yet in spite of the obvious severe grade of anoxemia, she was able to undertake fairly severe muscular exertion. This power of adaptation is remarkable. It may be considered analagous to the gradual acclimatization of individuals to the anoxemia produced by the lowered oxygen tension of the atmosphere in high altitudes.[4] As in polycythemia vera, the red cell count is raised. In this case it was 7,450,000. Counts as high as 12,000,000 have been reported. In this connection it might be of interest to note that such a high degree of viscosity of the polycythemic blood may sometimes produce a temporary thrombosis of the cerebral capillaries (Abbott) and give rise to curious epileptiform attacks. This doubtless explains symptoms in the case of Gilbert, the musician, already referred to. He was subject to dizzy spells and frequent headaches. Sometimes he was "thought to be intoxicated because he staggered in a faint spell." And later in his life there were "attacks resembling transient apoplexy, with weakness of the arm, hand or leg for a few hours or a few days, apparently passing off completely."

Oxygen-unsaturation and other blood findings are so characteristic that it is possible to diagnose a congenital heart lesion on these alone. In the recent German literature Uhlenbruck[13] reports a case confirmed by autopsy, where a diagnosis of pulmonary stenosis with interventricular septal defect was made purely on a basis of oxygen deficit in arterial blood, definite clinical symptoms, e.g., significant murmurs, being absent.

The characteristic dyspneic attacks seem to be caused by, and in proportion to, the ischemia of the pulmonary circulation.

Clubbing of fingers and toes, a prominent symptom, seems to be caused chiefly by stasis and lack of oxygenated blood with consequent effects on the tissues due to toxic products of metabolism which escape oxygenation. In this case there was chronic periosteitis but no new formation of bone.

With regard to the degree of disturbance of the circulation several factors must be considered. The degree of narrowing, whether simple

stenosis or complete atresia, is of prime importance. But one cannot judge the seriousness of the lesion from this alone. The seat and character of the stenosis and the presence or absence of an interventricular septal defect are also factors, so that in pulmonary stenosis an associated septal defect is unfavorable because its presence tends to reduce the volume of blood passing through the stenosed orifice and to permit the passage of venous blood into the arterial stream. But in atresia, where life is usually very short, an associated septal defect facilitates aeration, and there is less cyanosis and a better prognosis.[4] The present case falls into the class of extreme stenosis. From the standpoint of age attained, 16 years, it is unusual. In Abbott's series the average duration of life in all cases of pulmonary stenosis with defect of the interventricular septum was 10.8 years, and in atresia 3.4 years. In this case, besides the extreme conus narrowing other factors contributed to the seriousness of the lesion. There was a patent foramen ovale, the presence of which is unfavorable, probably because a smaller volume of blood is transmitted directly to the aorta. Also, the absence of a patent ductus arteriosus necessitates the blood supply to the lung proceeding by an even more devious route, a point to be discussed shortly.

In cases like the present one, it does not seem unreasonable to assume that the stenosis becomes relatively more marked with the growth of the heart after birth. With the establishment of a more or less efficient collateral circulation to the lungs the functional importance of the pulmonary conus becomes less. There is a decreased tendency for the passage to enlarge in proportion to the growth of the rest of the heart, especially as the rudimentary channel is lined by thickened endocardium surrounded by the heavy musculature of the right ventricle, which of necessity must develop a functional hypertrophy. In stenosis of a more distal part of the pulmonary tract, i.e., the artery at or above the valves, or one of the branches of the vessel, there is a tendency for the lumen to enlarge owing to the force of the blood on a thin walled structure, not as in the conus deformity surrounded by the constantly constricting musculature of the heart. Therefore, in marked conus stenosis, as time goes on, the relative functional importance of the pulmonary artery becomes less according to the degree and situation of the malformation. The lumen remains small, the walls thin and the valves delicate. In atresia the artery may be represented merely by a thin cord, as in the type well illustrated by Keith.[5] This relative progression of the anomaly would seem to be the chief factor to explain why it is that the majority of cases show few, if any, symptoms and no cyanosis at birth. Commonly this characteristic sign in morbus caeruleus becomes evident only after several weeks, months or, as is frequently the case, years after birth. Subsequently, cyanosis tends to increase rather than diminish. Thus, to instance the present case, the degree of stenosis at the age of 16 years was so extreme as to be almost an atresia and physiologically

must have acted practically as such; but earlier in her life the same sized opening would have permitted a relatively more normal pulmonary circulation. As the heart grows, the marked stenosis acts more and more like an atresia. If life be maintained, it is obvious that the compensatory or accessory pulmonary circulation is of prime importance. A brief consideration of this may be of interest.

Collateral Pulmonary Circulation.—When a widely patent ductus arteriosus persists, as is usual, the problem is simple. The blood flows from the right ventricle through the aorta a short distance and is distributed to the lungs by way of the ductus through the distal pulmonary radicals. But in many cases this fetal passage either does not persist or is not large enough to supply the needs of the lung, which must then rely largely on vessels separate from and not communicating with the main pulmonary stems.

A consideration of this is omitted or neglected in much of the literature on congenital pulmonary stenosis. Meckel was the first to suggest that in these cases the dilated bronchial arteries might carry on this function. Then Küttner[14] in 1878, proved by experiment that a very free anastomosis does normally exist between pulmonary and bronchial circulation in the lungs. His conclusions were disputed by some workers. Miller[15] in 1906, on the basis of experimental lung injection denied the existence of an anastamosis between the two systems. Others, however, have strongly supported the view of Küttner, notably Königstein.[16] But in the normal lung there is probably not as free a communication as Küttner at first thought. There is a very rapid breaking up of the pulmonary artery into capillaries. But unless almost the entire pulmonary supply to the lung is cut off, there is sufficient anastomosis with other branches of the pulmonary to compensate without the aid of the bronchials. Ghoreyeb and Karsner[17] have shown that the pressure in the pulmonary radicles must reach a very low level before the bronchial circulation is brought into service to compensate. Thus it would appear that the blood from the bronchial tree reaches the alveolar capillaries of the lung only in the greatest emergency when there is severe embarrassment of the pulmonary circulation. When this occurs, as in marked congenital pulmonary stenosis, the demand is urgent, and being present early in life, the bronchial arteries the more readily become enlarged and adaptable. The most extensive work bearing on this seems to be in the German literature, notably that of Christeller.[18] Searching the records of congenital pulmonary stenosis and atresia with closed or deficient ductus where the collateral pulmonary circulation was reported, he listed 26 cases, going back over a hundred years. Analysis of this shows that the bronchials were the most important, although sometimes other arteries shared or entirely assumed this special duty. He classified the vessels which may constitute the compensatory circulation as follows: (1) patent ductus arteriosus; (2) anterior bronchials; (3) posterior

bronchials; (4) anterior mediastinals; (5) posterior mediastinals; (6) esophageal; (7) pericardials; (8) coronaries; (9) anomalous arteries (e.g. from the aorta itself or from the subclavians).

In the present case it appeared that the bronchial arteries supplied the collateral circulation. Fig. 7 shows a portion of the thoracic aorta with the much enlarged superior left bronchial coming off just above the first paired aortic intercostals.

Christeller observed that a marked stenosis acts like an atresia, and he also points out that most patients die from intercurrent causes and not from insufficient circulation or heart failure.

Clinical evidences of an advanced subacute bacterial endocarditis were apparent in the case under consideration as soon as the patient came under observation. These accentuated rather than masked the congenital heart lesion. Cyanosis was very marked. Dyspnea was present. The loud rasping systolic murmur and other physical signs were pronounced.

The x-ray plate showed a relatively large, hypertrophied right ventricle. Owing to the serious condition of the patient only an anteroposterior plate was taken with a portable machine. This did not show the shadow of a second left arc which Abbott states is usually present, being due to the greatly hypertrophied conus of the right ventricle. The electrocardiographic tracings showing marked right ventricular preponderance were characteristic for cases of pulmonary stenosis. This preponderance was much in excess of that shown by any acquired lesion such as mitral stenosis.

There was surprisingly little dyspnea and orthopnea considering the very advanced vegetative endocarditis superimposed upon a heart already functioning under great difficulties. In spite of the extreme cyanosis the patient showed few signs of congestive heart failure. Hers was a "warm cyanosis." The heart compensated extraordinarily well until the bacterial infection overpowered it and, as demonstrated postmortem, invaded and ulcerated the heart muscle as well as the valves. This bears out the statement that most patients die from intercurrent causes and not from cardiac failure. This girl had a marked susceptibility to infection. She had had in addition the usual infectious diseases of childhood and smallpox. Reference has already been made to chorea from which she suffered about two years prior to her death. Some time prior to the onset of her fever and acute illness she had three teeth pulled. This seems of particular significance as pointing to a possible focus, the starting point of her final overpowering infection. In the examination of records of these cases it is striking how often infective foci precede death.

Fallot established the fact that a diagnosis of these cases could usually be made during life with a fair degree of certainty. The decided localization of murmur and often thrill, the increased cardiac dullness to

the right, the absence of pulmonary accentuation, and the presence of distinctive symptoms of congenital cyanosis, clubbing, dyspneic attacks, etc., often make possible a positive diagnosis. Patent ductus may give very similar signs, but in the latter there is usually pulmonary accentuation. The electrocardiogram and other methods mentioned previously are of course of much aid in diagnosis.

The prognosis in congenital heart disease is notoriously poor. It is, however, extremely variable and is affected by many factors. It depends first of all on the direct effect of the lesion upon the circulation and, consequent to this, the degree of oxygen unsaturation in the blood. In pulmonary stenosis with septal defect adult life is seldom attained, even with stenosis of a comparatively mild degree. The type in which the septum is closed gives a better prognosis. On the other hand with pulmonary atresia (and this case may almost be considered as such), the presence of a septal defect gives a relatively better prognosis than if it is closed. Yet even here nearly all patients die in early childhood. In Abbott's series the maximum age with pulmonary atresia, interventricular septal defect and patent foramen ovale was eleven years. The present case, therefore, although not strictly an atresia, would appear to be exceptional. Symptoms are a better guide to prognosis than physical signs. For example, a septal defect may give a marked murmur and thrill, yet lead to no hampering of the heart's action and to little interference with oxygenation, until some additional factor, such as obstruction in the pulmonary circulation, intervenes, producing a transient or terminal cyanosis. Persistent cyanosis, a continued low temperature and a high red cell count indicate a poor outlook (Abbott). Endocarditis is the gravest danger to all those who reach adolescence or early adult life.[9] And particularly is it so for such as the present. The danger of cerebral complications is greater than generally supposed. This is well brought out by Abbott,[6] who shows the great frequency of paradoxical embolism. In the case of Gilbert, cited above, who died of "apoplexy" with hemiplegia, death was due very likely, it is suggested, to this phenomenon, particularly as he had had repeated attacks suggesting embolism and since his blood pressure was always low and his arteries soft.

Another possible factor in the prognosis which, although not specifically mentioned by Abbott or others, seems to me of some significance is the collateral pulmonary circulation. In cases of marked stenosis or atresia, it would seem of considerable importance just where the lungs got their blood supply and how efficient this accessory circulation had become. For, as pointed out above, the route is much different when the ductus is closed.

It follows from what has been said about the danger of infections that patients with this disease must be carefully guarded against them. The social and economic factors must therefore of necessity be important

because where good hygiene prevails and the most suitable conditions of living are instituted the outlook is better.

SUMMARY

A clinico-pathological study has been made of a case of congenital heart disease exhibiting the complex known as the "tetralogy of Fallot," upon which was superimposed a subacute bacterial endocarditis with massive vegetations involving chiefly the tricuspid valve. Associated anomalies in both the heart itself (Chiari's network) and elsewhere have been discussed with reference to their bearing on the theories of the etiology and pathogenesis of congenital cardiac defects.

Special reference has been made to the collateral pulmonary circulation in the presence of extreme pulmonary stenosis or atresia when the ductus arteriosus is closed. A consideration of this has been neglected in most of the literature on congenital pulmonary stenosis. In such cases the enlarged bronchial arteries usually supply the blood to the lungs, although sometimes the pericardials, mediastinals, coronaries, esophageals, subclavians, or other arteries are called upon to assume this function. In the present case the bronchial arteries were greatly enlarged.

Aspects of the pathological physiology in the case are discussed with reference to the degree of disturbance of the circulation and its relationship to prognosis. The danger from infections is noted, particularly the extraordinary forms of vegetative endocarditis to which such cases are especially prone. Most patients die from intercurrent diseases and not from cardiac failure.

REFERENCES

1. White, P. D., and Sprague, H. B.: J. A. M. A. **92**: 787, 1929.
2. Peacock, T. B.: Malformation of Heart, Tr. Path. Soc., London, 1881.
3. Fallot: Marseille méd. **25**: 77, 1888.
4. Abbott, M. E.: Osler's Modern Medicine, Philadelphia, 1927, vol. 4, Lea & Febiger.
5. Keith, A.: Malformation of the Bulbus Cordis, Aberdeen Univ. Studies, **21**: 55, 1906.
6. Abbott, M. E., Lewis, D. S., and Beattie, W. W.: Am. J. M. Sc. **165**: 636, 1923.
7. Chiari, H.: Beitr. z. path. Anat. u. z. allg. Path. **22**: 1, 1897.
8. Hueper, W. C., and Berghoff, R. S.: Arch. Path. **6**: 1064, 1928.
9. Abbott, M. E.: Ann. Clin. Med. **4**: 189, 1925.
10. Boldero, H. E. A., and Bedford, D. E.: Lancet **2**: 747, 1924.
11. Lundsgaard, C., and Van Slyke, D. D.: Medicine **2**: 1, 1923.
12. Warthin, A. S.: Ann. Int. Med. **2**: 1225, 1929.
13. Uhlenbruck, P.: Ztschr. f. Kreislaufforsch. **19**: 601, 1927.
14. Küttner: Virchows Arch. **73**: 476, 1878.
15. Miller, W. S.: Anat. Anz. **28**: 432, 1906.
16. Königstein, H.: Anat. Hefte. **22**: 309, 1903.
17. Ghoreyeb, A. A., and Karsner, H. T.: J. Exper. Med. **18**: 500, 1913.
18. Christeller, E.: Virchows Arch. **223**: 40, 1916.

Department of Clinical Reports

THE ELECTROCARDIOGRAMS OF CORONARY OCCLUSION FOLLOWING A STAB WOUND IN THE LEFT VENTRICLE

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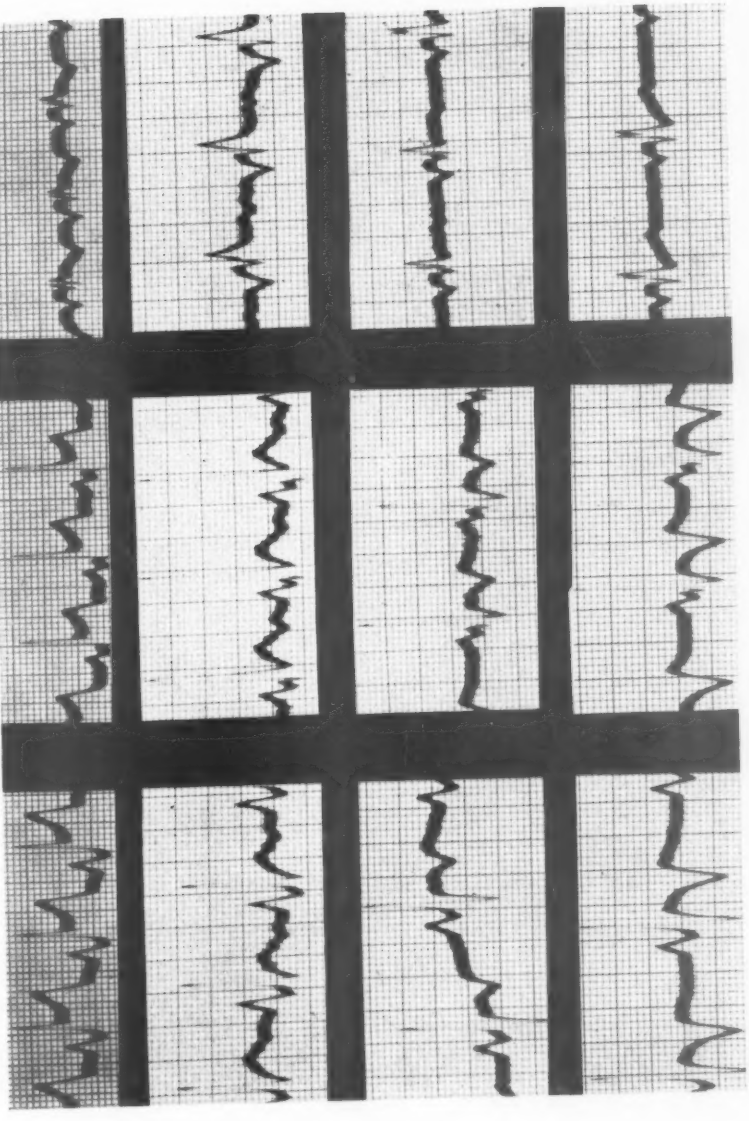
THE surgical aspects of this case were reported by Dr. Bates before the Philadelphia Academy of Surgery, January, 1929, and published in the Annals of Surgery, April, 1929. We will use his report and the further hospital records in summarizing briefly the history of this patient, and then present the electrocardiograms taken at weekly intervals, beginning five days after the injury and ending when they have returned to his normal.

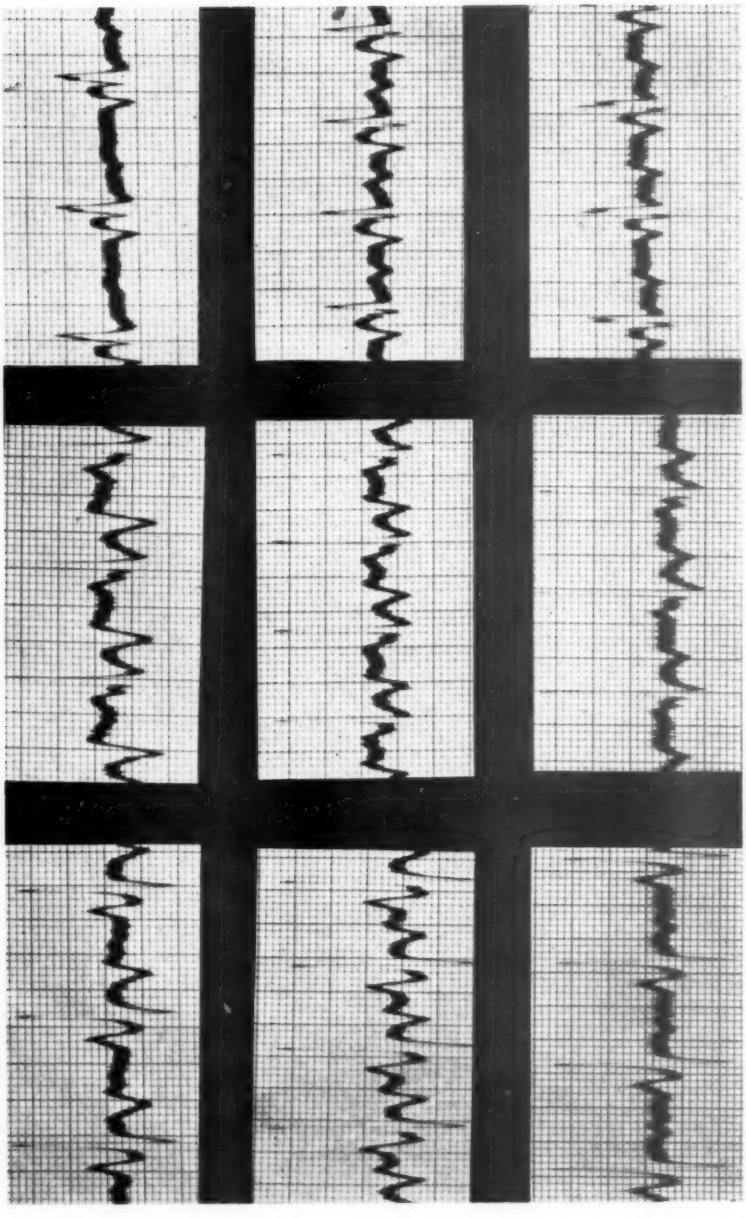
CASE REPORT

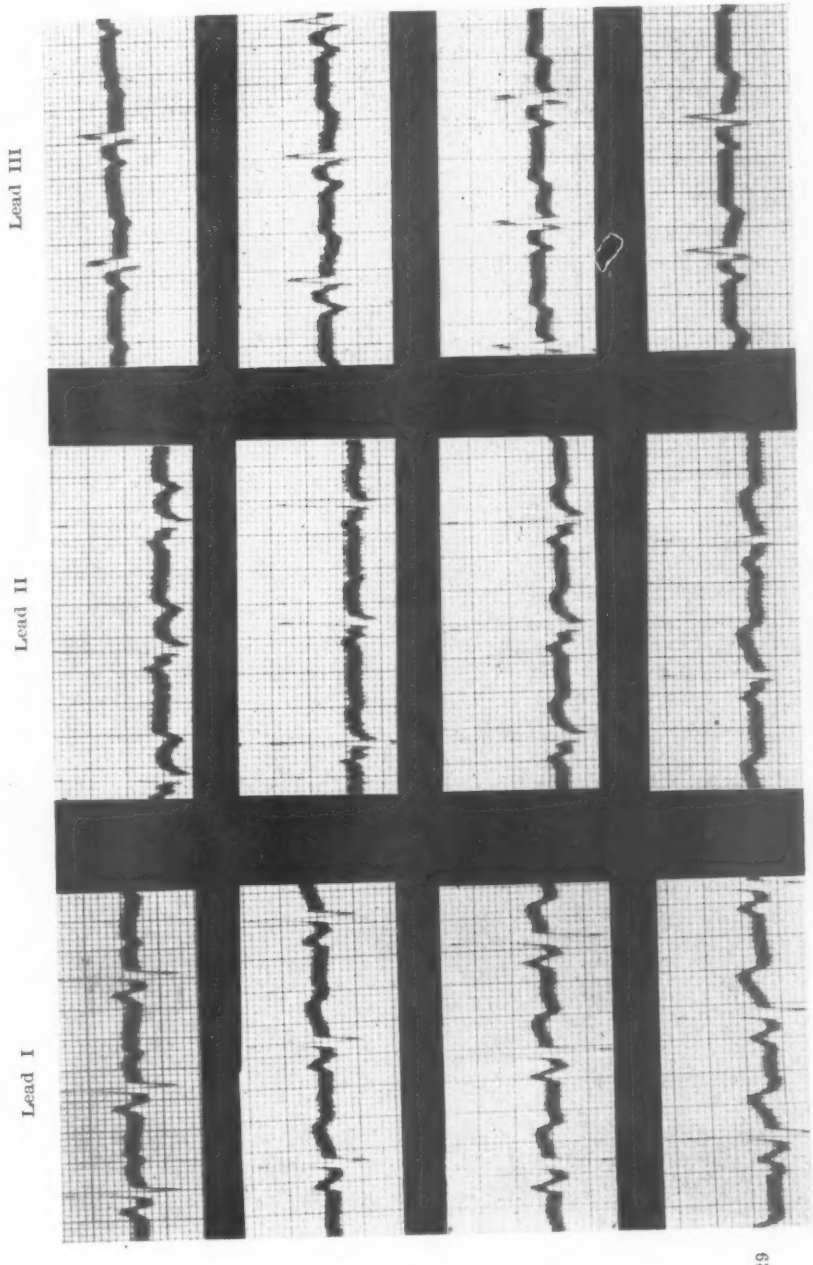
A young negro, 28 years old, was admitted to the accident ward of the Graduate Hospital at 1:15 A.M., on November 15, 1928. He had an incised wound in the anterior aspect of the left chest underlying a cut in the lapel of his coat, his vest, shirt and undershirt. The wound in the chest wall was about 1½ inches long, was vertical and just to the outer side of the left border of the sternum.

On admission the patient's temperature was normal, and his pulse 48. There was a loss of blood, but not large. The heart sounds showed a curious scraping or catching in the rhythm. The pulse rate quickly mounted, and the area of cardiac dullness rapidly increased, so that it was deemed advisable to explore the wound.

The vertical incision was enlarged upward and downward, and it was found that the knife had passed through the costochondral junction of the third and fourth left ribs. The intercostal muscles between the second and third, fourth and fifth ribs were severed, and the ribs were broken about 2 inches from their traumatic detachment. When an osteoplastic flap was laid back, the opening in the pericardium was easily seen. Bleeding was steady, and it was seen to be blood pumped from within the pericardium rather than from a cut vessel in the edges of the pericardium. Hemostats were applied to the two edges of the stab wound, and the pericardial opening enlarged upward and downward. Sponging cleared the field so that a hole in the left ventricular wall was visible over toward its right boundary and near its upper border. The knife blade had just missed the left coronary and its descending and circumflex branches, but it may have severed one or more of their branches in the heart wall. It was impossible to determine whether or not the wound connected with the left ventricular chamber, but from the amount of bleeding it was judged either that it did not, or else that there was a very small opening. The muscular bleeding was very steady, and with each contraction and rotation of the heart there was a steady spray of blood carried in the form of an arc on the table drapings above the wound.


Lead I
Lead II
Lead III
Nov. 20, 1928
Nov. 27, 1928
Dec. 5, 1928
Dec. 11, 1928


Lead I
Lead II
Lead III
Dec. 17, 1928
Dec. 27, 1928
Jan. 10, 1929


Lead I
Lead II
Lead III
Jan. 16, 1929
Jan. 23, 1929
Feb. 13, 1929
March 27, 1929

The wound in the ventricle was closed with a mattress suture. Following this a running suture was placed in the cut epicardium. The pericardium was then washed out with normal saline, and as the pericardial wound was being closed the heart stopped. It was slightly massaged by a finger through the wound, and 10 minims of a 1:1000 adrenalin chloride solution were given intramuscularly. Intravenous normal salt solution was then started. The pericardium was about closed when the heart again stopped. It was gently stroked by a finger inserted through the lower angle of the pericardial incision, adrenalin was run in with the intravenous saline, the heart rapidly recovered its normal rate, and there was no further trouble. Following this the external wound was closed.

During the time on the table the pulse rate never went over 108. The patient was in the hospital 27 days. His leucocyte count immediately following the operation was 10,200; and just prior to his discharge, 10,400. About ten days after the operation there was an exacerbation of fever, and the leucocytes rose to 19,000. At this time there was a pericardial friction rub and increase in the area of heart dullness. That there was pleuropericardial inflammation was also suggested by evidence of fluid at the left base. Soon after the development of the pericardial friction rub on November 26, 1928, the x-ray report showed a cardio-thoracic ratio of 19.5 : 29 cm., the left base line measuring 12.5 cm. The cardiac shadow showed general enlargement, but especially to the left. The left border of the heart appeared somewhat straightened, which may have been due to pericardial effusion; the aorta was not markedly enlarged, and the lungs showed no marked changes.

On December 1, 1928, the cardio-thoracic ratio was 15.5 : 28 cm. There was a marked diminution in the size of the cardiac shadow, and the lungs were clear.

On January 18, 1929, the cardio-thoracic ratio was reduced to 13.5 : 28.8 cm., which was apparently its normal.

The Wassermann and Kahn reactions were strongly positive in this patient, but he showed no evidence of change in aorta or valves, so that the lues was probably a comparatively recent event. The urine, the blood and blood chemistry were normal.

He was discharged to the out-patient clinic on December 12, 1928, but has been kept under constant observation since, and had an electrocardiogram taken weekly. At the present he shows no cardiac enlargement and no murmurs. There is no friction rub, but after exertion there is evident pulsation in the third and fourth interspaces adjacent to the left edge of the sternum, which suggests the possibility of some slight adhesions in that region. His blood pressure averages about 120 mm. systolic and 70 mm. diastolic. The heart rate and rhythm are normal. He feels well, and he has been doing light work around the hospital since his discharge.

A series of electrocardiograms are given showing the changes that went on from week to week until what appeared to be his normal curve had returned.

The first one was taken on November 20, 1928, five days after the injury and operation. In Leads I and II the T-wave came off high above the iso-electric line, and the curve was a typical picture of *acute* coronary occlusion.

In the curve taken November 27, 1928, Leads I and II showed the R-T interval started below instead of above the iso-electric line, but was still circumflex upward. Following it, the slight dip downward

in Leads I and II showed the beginning of the inverted T-wave of *chronic* coronary occlusion.

In the curve of December 5, 1928, Leads I and II showed the well-developed inverted T-wave of chronic coronary occlusion, which reached its maximum in the curve of December 11, 1928, and then began to decrease. The inverted T-wave disappeared more rapidly in Lead I than in Lead II, as was noted in the curves of January 10, 1929, and the following curves. The curve of March 27, 1929, apparently was his normal curve. The electrocardiograms have been taken every week since that time until July, and they have never varied essentially. Lead III has always shown the inverted P and T.

SUMMARY

The young man had a stab wound in the base of the left ventricle, in the region of the main branches of the left coronary artery. The wound was closed surgically, and he made a complete recovery. The first electrocardiogram, taken five days after the injury, was that of *acute* coronary occlusion. The second curve, taken twelve days after the injury was intermediate between the acute and chronic coronary occlusion. Twenty days after the injury T_1 and T_2 showed the typical inverted T-wave and circumflex upward R-T interval of *chronic* coronary occlusion, which reached its maximum twenty-six days after the injury; after this time the inverted T_1 and T_2 began to recede and had reached the normal upright T on March 27, 1929, that is, eighteen weeks after the wound and operation.

PULMONARY STENOSIS WITH BACTERIAL ENDOCARDITIS IN AN ADULT*

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CASE REPORT

CHIEF COMPLAINT.—A woman, 32 years old, was first seen on March 12, 1925, complaining of the fact that all her life she had been unable to play games or hurry without dyspnea, and for the past year this dyspnea had increased in severity and frequency. She also complained of lack of energy and inability to sleep.

Family History.—Negative, except that her husband had died of tuberculosis.

Past History.—She had had measles, chicken pox, mumps and a severe attack of scarlet fever. She had pneumonia when a year old. The family doctor also told her parents that she had heart trouble when she was a year old. At fourteen years of age she had rheumatism. No detailed history of this was obtained. There was no history of tonsillitis or chorea. She had had a chronic cough for years but no expectoration or hemoptysis. Her appetite was poor. There was also an irregular menstrual history. There had been one normal pregnancy.

Present Illness.—She had always been troubled with dyspnea on slight exertion as long as she could remember, and for the past year this dyspnea had increased in severity and frequency. No edema, palpitation or precordial pain was ever present. She had never noticed anything peculiar about her color. Her other complaints at this time were lack of energy and inability to sleep. In the past year she had lost 26 pounds and had not felt particularly well since two wisdom teeth had been removed some months previously.

Physical Examination.—Positive findings: The patient was a thin, pale blond woman. The veins of her neck were distended. On percussion the heart was moderately enlarged, the apex was visible just outside the nipple line, with a marked apical pulsation and a definite thrill over the mitral area. The rhythm of the heart was perfectly regular; the rate 92. There was a loud blowing systolic murmur over the entire precordium, most marked over the pulmonic area, transmitted to the left. At times a presystolic murmur was heard over the mitral area. The systolic pressure was 110 mm. and the diastolic 70 mm. The liver was felt two fingers below the costal margin. At this time the red blood cell count was 6,300,000; white blood cells 8,000; hemoglobin 70 per cent. The chemical examination of the blood was normal.

The electrocardiogram showed normal sinus rhythm. The conduction time was normal. Very marked right ventricular preponderance was present. The P-wave was abnormally large and the T-wave was inverted in Leads II and III.

The Wassermann reaction of the blood was negative, and the urine examination at this time was completely negative.

A radiographic examination of the chest at this time showed moderate hypertrophy of the pulmonary arc and of the right and left sides.

*Presented, in abstract before the Annual Meeting of the New York Pathological Society, at the N. Y. Academy of Medicine, January 10, 1929.

Clinical Course.—The patient went to California in September, 1927, where she had restful out-of-door life, but her cardiac reserve was noticed to be considerably less. When she returned in February, 1928, it was noticed that her dyspnea had increased and that her pulse was more rapid—rate 120. Also she was extremely nervous at this time. She was seen several times during February and complained a good deal of a hacking cough.

On March 1, 1928, she was carefully examined, and at this time her spleen and liver were easily felt. She went to Florida where she stayed about six weeks. At this time she was not sleeping so well, and her reserve had greatly decreased. She was able to do very little except to remain quiet and out of doors. She then went to Atlantic City where she was put to bed for a cough. It was

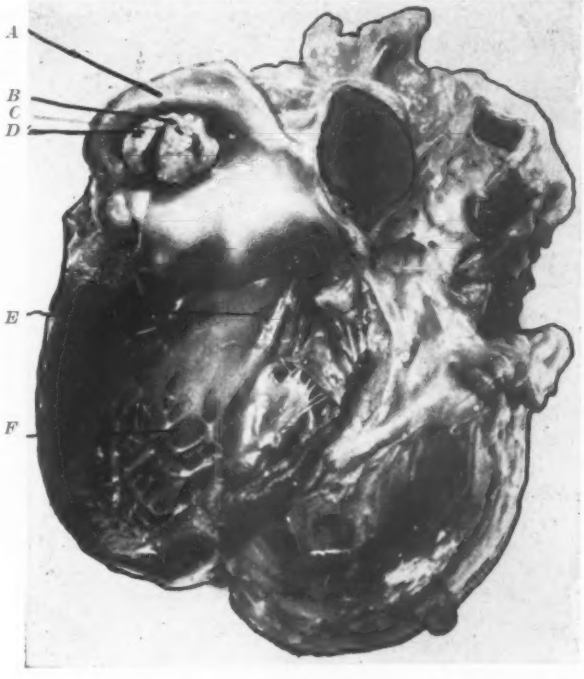

Fig. 1.—View looking down on pulmonary valves. *A*, pulmonary artery, stenosed (opened, showing intimal surface); *B*, orifice of pulmonary valve (8 mm. × 2 mm.); *C*, long granular vegetations in umbrella fashion; *D*, pulmonary valves joined at raphe borders; *E*, mitral valve leaflet; *F*, left ventricle, opened.

noticed at this time that her spleen and liver had become greatly enlarged. No record was kept of her temperature.

On September 11, the following physical examination was made after she arrived in New York:

Positive Findings.—The mucous membranes were pale and a small petechia was observed in the right conjunctiva. The spleen was hard, firm and greatly increased in size, reaching almost to the umbilicus. The liver was about two fingers below the costal margin. The cardiac examination was the same as had previously been observed. It was noticed at this time that she was running a temperature, varying between 100° and 104°.

Laboratory Findings.—Blood cultures, September 13 and 15. No growth. Blood count: red blood cells, 3,950,000; white blood cells, 6,500; hemoglobin 60 per cent; urine, many red blood cells and a few granular casts.

During the next two and a half months her condition was progressively more septic. There was no clinical evidence of infarction, except that she complained a good deal of cough. Edema of the legs and vulva was noticed, which spread upward to the thighs and back. She complained a good deal about bleeding from her nose, and she had intermittent attacks of bloody diarrhea. On November 13, 1928, a purulent discharge was noticed coming from the vagina. A vaginal examination was made, but there was no evidence of localized abscess. Petechiae in various parts of her body at this time were noted. On November 28, a generalized petechial rash appeared over her entire body, and she became stuporous and irrational. This rash faded somewhat during the following week. On December 2, she died suddenly.

Ante-Mortem Diagnosis.—Chronic cardiac valvular disease; mitral stenosis and insufficiency; cardiac hypertrophy; subacute bacterial endocarditis; infecting organism unknown.

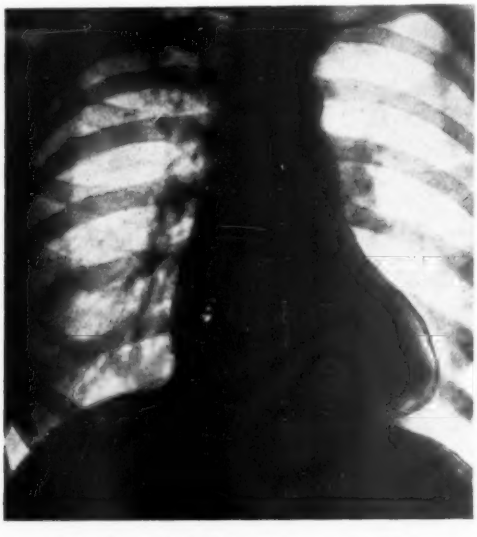

Fig. 2.—Teleroentgenogram of chest.

(Diagnostic note.) On first examination, the notes show that a diagnosis was made of "probable congenital lesion." This was founded primarily upon the following: a loud pulmonary murmur, the history obtained, and the electrocardiogram which was quite characteristic. This diagnosis was never revised. The patient drifted into the group of mitral cases, and the original classification was more or less in the background.

Summary of Autopsy Performed on December 2, 1928, at a Private Undertaker's Establishment.—Heart. The pericardium is slightly bulging. The contents consist of about 40 c.c. of fibrinous, flaky serum. The visceral and parietal layers show a shaggy hair-like exudate. There are a few easily broken-down adhesions about the basal portions. The heart weighs 280 gm. and is greatly enlarged in its right chambers, the apex being formed by the right ventricle, the left not appearing on the anterior aspect. A striking feature of the organ is the marked dilatation of the right auricle and the distinct hypertrophy of its wall, the columnae carneae being held out in bold relief. A small foramen ovale is closed. In the posterior auricular wall, just about the orifice of the coronary sinus, are two saccular, pocket-like adhesions, with a rounded muscular fence with muscular

puckerings. The valve at the orifice of the coronary sinus is lengthened, measuring 1 cm. The tricuspid orifice in circumference is 9.6 cm. The cusps are moderately but evenly thickened. There are slight nodular thickenings just behind the free margin of the cusps at the attachment of the chordae tendinea but the chords themselves are neither thickened nor shortened. There are a few firm, warty, calcific nodules, 4 cm. in diameter on the auricular surface of the leaflet. The right ventricle is astonishingly hypertrophied, the wall measuring 2 cm. in thickness through the region of the conus arteriosus. The papillary muscles, particularly the pectinate muscles, are very prominent and enlarged. The musculature of the

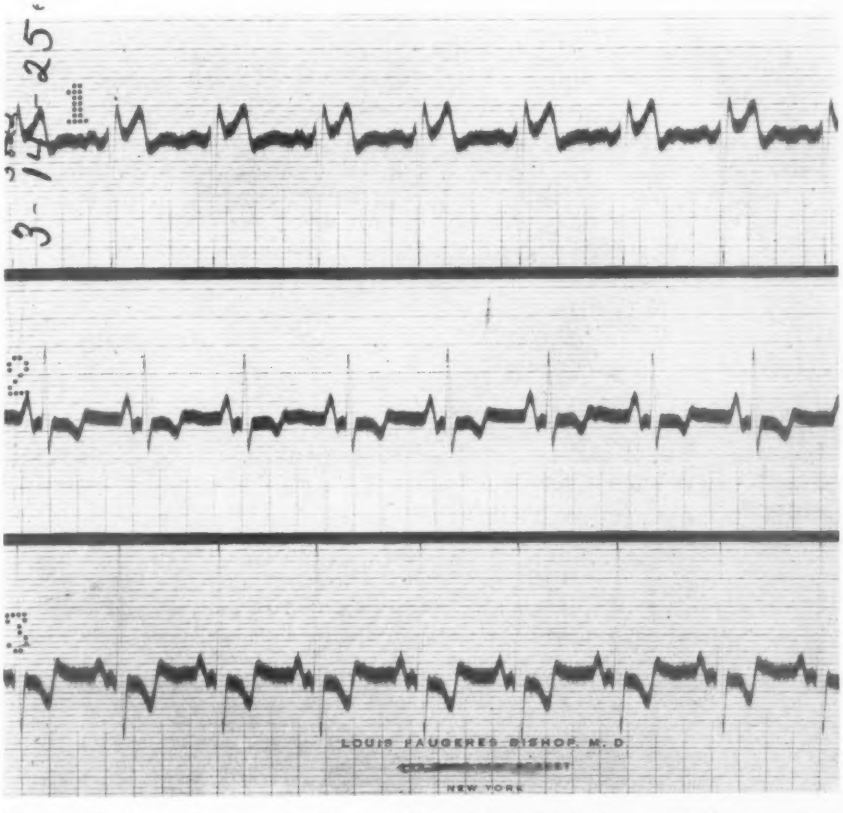

Fig. 3.—Electrocardiogram showing marked right ventricular preponderance characteristic of congenital heart disease, and inverted T-wave in Leads II and III.

conus arteriosus is particularly hypertrophied, having short longitudinal folds. The circumference of the conus is 4 cm. in its midportions. The endocardium of the entire right ventricle is thickened, opaque and white. The pulmonary orifice measures at the bases of the pulmonary valves 3.75 cm. in diameter. The pulmonary artery is thin-walled. The pulmonary cusps are firm along the contiguous borders, with symmetrical edges, leaving a slit-like orifice 8 mm. long and 2 mm. wide. There is a small raphe showing the attachment of the cusps to each other Across the rim of the valve is a tapering growth of long, granular, greyish vegetations, forming a torn umbrella-like structure. One of these growths is particularly long and tenuous.

The left ventricle appears normal. The walls of the attachment of the posterior

mitral leaflet measure 1 cm. in thickness. Section of the myocardium shows it to be fine and smooth, but irregularly interrupted by pearly grey, diffuse, irregular areas of fibrous change. The mitral orifice is 9 cm. in diameter, the leaflet is entirely normal. The aortic orifice at the base of the semilunar valve measures 5 cm. The aortic cusps are normal in shape but show a line of calcification around the lunulae. The intima of the aorta is smooth and elastic.

The lungs are congested posteriorly. There are a few small, round, raised lumpy patches in the posterior parts of the posterior lobes. Scattered throughout are irregularly bordered dark red areas of partially consolidated tissue with no pleural involvement. The spleen weighs about 900 gm. and has normal general configuration. No congenital notches are observed. Seen through the capsule the organ is a dense purple red color, firm and elastic. On section it is firm, cuts easily, and is of dark red color. Many splenic follicles are seen but no infarcts. The liver weighs approximately 2000 gm. and has a typical "nutmeg" appearance, very dense and firm. The kidney is normal in size and configuration, and of a smooth, dark purple color. Dense, mucous, dot-like areas are scattered throughout the surface and interior of the cortex. On section these are found to be confined to the zone glomeruli.

Microscopical Examination.—Lungs: lobular pneumonia; no infarcts. Liver: advanced chronic passive congestion. Kidney: glomerular nephritis. Spleen: chronic passive congestion. Heart: fibrinous pericarditis with slight reaction in subserous layers; few leucocytes; areas of wide fibrosis in the myocardium; no Aschoff bodies; coronary arteries show no sclerosis.

COMMENT

On account of the fact that cases of pulmonary stenosis reaching adult life, without other congenital heart disease, are relatively rare, we believe they should be recorded. This case is of special interest because the patient lived to adult life and then died as the result of bacterial endocarditis. The infecting organism was not identified.

NOTE.—Unfortunately, due to the fact that this autopsy was done at some disadvantage we did not remove enough of the aorta to include the ductus arteriosus. We have had a personal communication from Dr. Maud Abbott, concerning this case, who tells us that it is very probable that the ductus arteriosus was closed.

Department of Reviews and Abstracts

Selected Abstracts

Burwell, C. Sidney, Smith, W. C., and Neighbors, DeWitt: The Output of the Heart in Thyrotoxicosis With Report of a Case of Thyrotoxicosis Combined With Pernicious Anemia. Am. J. M. Sc. **178**: 157, 1929.

A case of thyrotoxicosis complicated by pernicious anemia is reported. The increased demand for oxygen combined with the decreased oxygen carrying power of the blood was met by a great increase in the cardiac output per minute and hence in the work of the heart. Repeated observation of the cardiac output in this case and in a second case of thyrotoxicosis revealed that the adjustment of the circulation to increased demand for oxygen took place by an increase in cardiac output rather than by an increased utilization of the arterial oxygen. When the metabolic rate was highest and the hemoglobin lowest, the cardiac output was approximately 20 liters per minute, an amount ordinarily associated only with severe and short lasting muscular exertion: Following the administration of iodin, the basal metabolic rate, pulse rate and cardiac output all fell while the body weight increased. The question of the effect of digitalis in thyrotoxicosis is not cleared in any degree by these observations.

Schwartze, E. W., Hann, R. M., and Keenan, G. L.: Ouabaine, Physiological Standard for Digitalis, Strophanthus and Squill. J. Pharm. and Exper. Therap. **36**: 481, 1929.

As a result of the investigations herein reported, the suggestion was made that in the Revision of the U. S. Pharmacopeia the form of official Ouabaine be changed from that crystallized from water and containing 20 per cent moisture to that crystallized from alcohol to which a little ether has been added and containing approximately 12.5 per cent moisture. This suggestion was adopted by the Committee.

Gross, Louis, Loewe, Leo, and Eliosoph, Bingam: Attempts to Reproduce Rheumatic Fever in Animals. J. Exp. Med. **50**: 41, 1929.

Experiments are described in which an attempt is made to reproduce in animals the lesions characteristic of rheumatic fever in the human. A large number of animals representing 7 species was employed. Among other materials streptococci isolated in pure culture from the blood of rheumatic patients as well as whole blood, plasma, serum, pericardial, pleura and hydrocele fluid, filtrate from tonsils, subcutaneous nodules, lymph nodes and nasopharyngeal washings obtained from such patients were used in a variety of combinations and with a number of procedures calculated to predispose the animal to the disease.

The criteria are given, the fulfilment of which is essential for the establishment of the experimental production of rheumatic disease in animals. These criteria are the reproduction of (1) the Aschoff body, (2) nonbacterial pericarditis (3) nonbacterial verrucous endocarditis. Judged by these criteria, the authors have failed to reproduce the disease and they believe this is true of all the work thus far reported in the literature.

Saphir, Otto: Involvement of Medium-Sized Arteries Associated With Syphilitic Aortitis. Am. J. Path. 5: 397, 1929.

The present study was undertaken as a search for initial or early stages of syphilis in types of vessels whose structures closely resemble that of the aorta. Fifty cases which at autopsy showed grossly and histologically syphilitic lesions in the aorta were used. The innominate artery showed syphilitic changes in 33, the carotid in 29, the superior mesenteric in 10, the inferior mesenteric in 3, the common iliac in 10 and the femoral artery in 7 cases. The subcutaneous artery was examined in 29 cases, 15 of which showed syphilitic lesions.

The syphilitic lesions were characterized by endarteritis of the vaso vasorum and perivascular infiltration of lymphocytes in the adventitia. The media of the elastic type of artery showed an interruption of the continuity of the elastic fibers and fibrotic areas combined with circumscribed lymphocytic infiltration. The media of the muscular type of arteries only rarely showed changes. In the intima circumscribed button-like areas of fibrosis without degenerative changes were found very frequently. These are not specific but are chronic inflammatory in nature and might be associated with any type of pathological lesion in the adventitia.

Paisseau, G., and Oumansky, V.: Intermediary Forms Between Rheumatic Endocarditis and Malignant Endocarditis. Arch. d. mal. du coeur. 22: 652, 1929.

Rheumatic endocarditis produces valvular sclerosing lesions and the results after long years are mechanical, with insufficiency and final failure. Malignant endocarditis which is most commonly grafted on old valvular lesions is essentially an infectious disease with a fatal prognosis showing septicemic manifestations, e.g., anemia, emboli, purpura and Osler's nodes, while the cardiovascular symptoms are less prominent.

In rheumatic endocarditis no causative organism has been proved, while in malignant endocarditis one constantly finds the streptococcus of Schottmüller. This latter though grown with difficulty on the usual media has two characteristics: It is only slightly hemolytic, and it is not pathogenic for animals, though typical lesions can be produced if the valves are first traumatized or if the virulence is raised by repeated transfer. However, there seem to be varieties of endocarditis intermediary in form which have characteristics of both types. Cases of rheumatic endocarditis have been noted which instead of terminating in the usual way with cicatrization show themselves capable of developing the characteristic cardiac changes but without the articular symptoms.

The author quotes Clawson's beliefs on the identity of the organisms of malignant endocarditis and rheumatic endocarditis and the ease of culture of organisms in the latter condition by his own method.

The author believes that those bacteriological findings are in accord with the clinical picture of the disease.

Rheumatic endocarditis is usually accompanied by signs of cardiac insufficiency. There is an absence of splenic enlargement of emboli, and the disease responds to salicylate therapy. On the other hand, in endocarditis lenta the opposite holds, and there are no pleural or pericardial manifestations. However, the value of none of these individual signs is absolute. Salicylates frequently have no effect on the cardiac lesions of rheumatism. Forms of malignant endocarditis exist where cardiac failure does occur and evidences of infection are often slight. Infectious emboli have been observed in rheumatic endocarditis, and Bambonneix has also noted the presence of Raffin-Osler nodes.

The author quotes four cases which support his belief. The first two were sisters from a family of eight. Three had had attacks of acute articular rheumatism and

one of erythema nodosum with articular symptoms. One of the rheumatic subjects died with symptoms resembling infectious endocarditis. Of the other two rheumatic patients, the eldest after history of articular rheumatism developed classical malignant endocarditis of which she died. Embolism of the lungs, kidneys, and spleen was present; the anemia was intense; blood cultures were negative. Autopsy, however, showed no vegetative endocarditis, very little scarring of valves with a large clot partly organized in the left auricle. The younger sister during an attack of acute articular rheumatism suffered numerous bouts of severe purpura. Exophthalmic goiter also developed which was apparently incidental. In this case the purpura and anemia made one think of malignant endocarditis. The consistently negative blood cultures placed it in the class of recurrent rheumatic endocarditis.

Two other examples are cited where purpura was a prominent symptom and where the case did not respond to salicylates. The first, a boy fifteen years old, was a member of a family where three others had suffered from rheumatic heart disease. Purpura and a severe aortic lesion were the outstanding lesions. The second case, a girl twenty-four years old, was seen in her third attack of acute articular rheumatism. Blood cultures were negative, but a purpuric eruption appeared which became spreading and ecchymotic. This became generalized and lasted one month. A pericardial rub was present and an interlobar pleurisy, both of which resolved.

Both cases showed purpura as an outstanding feature. This symptom, though it occurs, is rare in rheumatic heart disease and especially in acute articular rheumatism.

All four cases showed characteristics common to rheumatism and malignant endocarditis. It is possible that in the evolution of the disease a stage is reached which it is impossible to classify as either disease. Diagnosis then rests on autopsy findings or on the recovery of the patient.

Agostoni, G.: A Case of Right Bundle Branch Block Suspected Clinically, Diagnosed With the Electrocardiogram and Proved by Autopsy. Arch. d. mal. du coeur. 22: 577, 1929.

The case observed was that of a man aged twenty-six years, complaining of palpitation and dyspnea on effort. His previous history was not important. The general appearance was good excepting for slight cyanosis of the lips and some dyspnea. Examination of the circulation showed a rapid pulse with occasional extrasystoles. Blood pressure was 100/70-80. A triple rhythm was present especially over the ensiform and due to reduplication of the first sound. At the base the second sound was accentuated over the pulmonary area where there was also a short, soft, diastolic murmur. Orthodiagram showed enlargement of the entire heart with enlargement of the pulmonary hilus. The jugular veins were distended, the liver was enlarged, and slight edema of the lower extremities was present. Wassermann was negative and only a trace of albumin was present in the urine. Triple rhythm without the characteristics of gallop rhythm lead the authors to consider a branch lesion. The electrocardiogram confirmed this. The R-S interval was prolonged. The R-wave being upright in Lead I, inverted in Lead III with the T-wave oppositely directed. Splintering of R I was also noted.

The diagnosis of this lesion was based on a greatly enlarged heart without particular shape, the absence of valvular lesions, the presence of arterial hypotension. Radioscopically the chief points were those of "danse hilaire," that is movement of the hilus shadows with the cardiac contractions. On this sign and the presence of diastolic basal murmur a diagnosis of functional pulmonary insufficiency was based.

At autopsy, it was found that the heart was very big, with the myocardium showing greyish white streaks on section; the endocardium was normal, the pulmonary artery dilated. Histologically the right branch was interrupted in different areas by cicatricial tissue.

The etiology was presumed infectious and possibly of rheumatic origin.

Reid, William D., and Kenway, Florence L.: Electrocardiographic Signs Associated With Low Basal Metabolism. Endocrinology **13**: 191, 1929.

No electrocardiographic findings characteristic of low basal metabolism were found in a study of 260 low basal metabolic cases, 260 normal basal metabolic cases and 70 high basal metabolic cases. The changes usually described as occurring in such cases were not found frequently enough to be characteristic. In five untreated cases of myxedema all showed low T-waves, and 4 showed low P-waves as well. R-waves less than 0.5 millivolts were found in three cases, and in each of the remaining two the R-wave equaled 1 millivolt.

Bowers, L. G.: Pericardiotomy for Pyopericardium. Arch. Surg. **19**: 301, 1929.

Report is made of a boy aged seventeen years with purulent pericarditis associated with empyema, the result of a left-sided lobar pneumonia. A large amount of pus was aspirated from the pericardium, cultures from which showed pneumococci. Pericardiotomy was performed four weeks after the onset of the acute illness. There was immediate relief, though the patient died one week after the operation with sepsis. The autopsy showed a left empyema, pneumococcus type; complete atelectasis and unresolved pneumonia of the left lung; fibrinopurulent pericarditis; organizing right-sided adhesive pleuritis. A special operative procedure used on the patient is described and presented with the hope that it will stimulate other trials. The author believes that pericardiotomy is a simple operation presenting little or no risk and is capable of saving life.

Two factors are in operation which constitute a serious handicap to the heart's work: first, the degenerative effects in the myocardium produced by the local inflammatory process; second, the mechanical handicap produced by the rapidly increased imprisoned exudate within the sac.

Simon, H.: Plethysmographic Studies of Rhythmic Changes in Vessel Size. Ztschr. f. Kreislaufforsch. **15**: 448, 1929.

Studying the spontaneous variations in the volume curve of a rabbit's ear, Simon finds that under similar conditions both ears show the same type of rhythmic change. When the experiment is prolonged and the animals are not kept sufficiently warm, these variations gradually diminish together with a diminution in the total ear volume. In this state, the contracted ear vessels fail to respond to skin stimuli. However, by warming the animal, these rhythmic changes are again brought forth, and the vessels again assume their reflex excitability.

The rhythmic changes disappear after section of the cervical sympathetic, including the stellate ganglion. This procedure causes marked increase in the ear volume on the ipsolateral side.

When one ear alone is warmed from 47° to 50°, the other ear shows a marked increase in total volume, without the appearance of rhythmic changes, however.

When the carotid blood supply was cut off temporarily, a postanemic hyperemia was observed only in normal ears, not in denervated ears.

Schwentker, Francis F., and Noel, William W.: The Circulatory Failure of Diphtheria. Bull. Johns Hopkins Hosp. **45**: 276, 1929.

In an analysis of 1600 consecutive cases of diphtheria admitted to the Sydenham Hospital from 1920 to 1927, there were 178 deaths. Of these, 139 followed laryngeal diphtheria while the remaining 39 were definite clinical cases of circulatory failure. According to the clinical course and the findings at autopsy, the authors believe that the evidence allows a classification of circulatory failure of diphtheria into two groups, early and late. This classification is based not on the time of onset of failure but on the appearance of the patient. The cases of early circulatory failure are an essential part of the diphtheria intoxication and are the end-stage of the disease, the result of a virulent infection and too often of neglect on the part of the parents to summon a physician until the condition has become alarming. Vasomotor collapse with toxemia forms the outstanding picture.

Cases of late circulatory failure occurred as early as the eighth day of the disease but usually ten to twenty days after the onset. The usual course was that after a week or more of apparent convalescence, the patient suddenly complained of symptoms referable to the heart. There were disturbances of cardiac rhythm with evidence of congestive failure; death was often very sudden. Thus late circulatory failure is a complication of the disease caused probably by local inflammatory reactions incident to regeneration and repair in the cardiac tissue.

Oettinger, Jacob: Electrocardiographic Changes After Acute Coronary Occlusion. Ztschr. f. klin. med. **110**: 578, 1929.

In two cases of acute coronary thrombosis, one of which was confirmed by autopsy, the author found the following electrocardiographic changes:

1. In one case, during the first few days following the occlusion, there was an abnormal elevation of the R-T interval above the base line, the T-wave rising directly from the upper half of the descending limb of the R-wave and merging into the next P-wave. On the sixth day after the occlusion, Lead I showed a sharp inversion of the T-wave.

2. In the second case, low amplitude of the ventricular complex was found with similar changes in the R-T interval.

A note is made of a case of mitral stenosis in which an antemortem diagnosis of coronary embolism, established by electrocardiographic studies, was confirmed by autopsy. This case will be reported elsewhere.

Due credit is given to American workers for their early recognition of coronary thrombosis as a clinical entity.

Jones, H. Wallace, and Roberts, R. E.: The Electrical Axis of the Heart as an Indicator of Changes in Ventricular Predominance. Quart. J. Med. **23**: 67, 1929.

The authors have studied the effect of ventricular preponderance on the form of the electrocardiogram in several groups of cases. In order to give a mathematical value to different degrees of preponderance, the calculation of the electrical axis of the heart has been determined by the formula and graphic method proposed by Carter, Richter and Greene. The first group of cases studied showed the effect of respiration and posture on the electrical axis of normal hearts. The group showed that these two factors usually produced profound changes in the position of the heart and form of the electrocardiogram.

In cases where there is a fixed apex beat clinically, due to adherent pericardium, the movements of the electrical axis with respiration show by contrast with the

normal cases no marked difference. Instead of the rotation in direction of the axis with deep inspiration and expiration, there is only an extremely small movement, a striking result which provides a valuable test for this lesion. In this group of cases, the authors feel that the change in the electrocardiogram which took place following shift in position of the patient from the right and left side was small.

Cases in which there is complete transposition of the viscera show with the electrocardiogram marked evidence of right-sided preponderance. When the respiratory movements of this group are examined, they are found to be similar to those found in normal individuals except that rotation is in the opposite direction. A recognition of this right-sided preponderance in the first few weeks of life and its return to normal at the end of three months in healthy children is of importance in the early recognition of congenital cardiac disease by persistence beyond the normal period of evidence indicating right-sided preponderance.

In a group of 17 cases with changes in ventricular preponderance with alteration in the cardiac rhythm, the authors found that no change in preponderance took place with the change in rhythm in 10 cases, while the remaining 7, with one exception, showed more evidence of right-sided predominance when the heart was fibrillating than when it was beating with a normal rhythm.

Hughes, F. W. Terrell, and Perry, C. Bruce: Senile Arterial Changes in a Child Aged Seven Weeks. Bristol Med. Chir. J. **46**: 219, 1929.

A child, aged seven weeks, suddenly died following a short period of cyanosis and distressed breathing. Post-mortem examination showed a heart normal in size but with marked thickening and tortuosity of the coronary arteries which stood out from the rest of the heart like cords. The valves were normal. On microscopical examination, the coronary arteries showed more or less obliteration by extreme intimal thickening composed of a loosely arranged fibrillar connective tissue. The media was almost completely calcified and only very broken fragments of muscle fibers were left. This change was confined to the larger branches of both coronary arteries, the smaller arteries being normal. Scattered throughout the myocardium were areas of early fibrosis replacing the muscle fibers.

The family history and previous history of the child showed no etiological condition. Wassermann on the mother's blood was negative.

Holt, Evelyn: Chronic Adhesive Pericarditis in Childhood. Am. J. M. Sc. **178**: 615, 1929.

The present study is an attempt to follow over as long a period as possible 51 children who have had acute pericarditis or in whom a tentative diagnosis of adherent pericardium has been made. In 39 of the cases there is a definite record of some pericardial involvement, 22 cases are still under observation, 21 have died with 5 autopsies, and 8 have been lost. A detailed analysis of the individual cases follows.

A summary of the clinical course indicates that rheumatic infection occurred in a large number of the children, usually in children at an early age, and was characterized by repeated acute attacks. In 26 of the cases an attack of pericarditis seemed to be a definite turning point, the beginning of a train of unfavorable signs and symptoms, which became progressively worse and usually led to death within a short time. Of the 21 who died all had symptoms and signs of cardiac insufficiency, and in practically every case the apparent cause of death was cardiac failure. The cases showed evidence of continued cardiac infection and progressive damage. The ascites present in 12 patients was associated with cardiac decompensation, and the picture was that of cardiac failure rather than cirrhosis or pseudo-

cirrhosis of the liver (Pick's disease). Auricular fibrillation was observed in 6 of the children. In 4 cases it appeared as part of a general breakdown preceding death. Bacterial endocarditis was present in only 2 of the cases.

The main physical signs associated with adherent pericarditis are described. It is pointed out that adherent pericardium is one form of heart disease most likely to come to the autopsy table undiagnosed. The history of acute pericarditis, the marked increased size of the heart out of proportion to the supposed endocardial or myocardial damage, systolic retraction of the interspaces along the chest wall, fixation of the heart in its position, interference with respiration, dilated veins over the chest wall, occasional pulsus paradoxus are all discussed. Pericarditis is associated with valvular disease usually with mitral stenosis and often with aortic insufficiency.

Clawson, B. J.: The Aschoff Nodule. Arch. Path. 8: 664, 1929.

In this extensive review, the author has attempted to correlate the description of Aschoff bodies as given by different observers and to compare their observations with the material in 50 cases from his own group. He discusses the significance of such a structure in the diagnosis of acute rheumatic fever and concludes that it is doubtful whether the Aschoff nodule should definitely be considered a specific lesion resulting from a specific rheumatic virus. The theories on which the formation of the Aschoff nodule may be formed are discussed.

Nabarro, David, and MacDonald, R. A.: Bacteriology of the Tonsils in Relation to Rheumatism in Children. Brit. M. J., October 26, 758, 1929.

A bacteriological study has been made of the tonsils removed from 50 rheumatic and 48 nonrheumatic children. The streptococci recovered from the tonsils were studied quantitatively and qualitatively as to their various characteristics. No material difference was found to occur between the organisms recovered from the two groups of children. The authors believe that this absence of difference fits in with the theory that there is no specific streptococcus which is the cause of rheumatism but that the condition is due to a hypersensitiveness resulting from repeated small doses of toxin.

In spite of the lack of difference, tonsillectomy in rheumatic cases is probably a valuable prophylactic and therapeutic measure.

McClenahan, W. U., and Paul, J. R.: A Review of the Pleural and Pulmonary Lesions in Twenty-Eight Fatal Cases of Active Rheumatic Fever. Arch. Path. 8: 595, 1929.

The material in this study is based on 28 fatal cases of acute rheumatic fever showing signs of activity in the myocardium or endocardium. Active pericarditis was present at autopsy in 75 per cent and active pleurisy in 64 per cent of the cases. Pleurisy apparently is a specific manifestation of the rheumatic infection and is characterized by the nonsuppurative character of the exudate and absence of bacteria. This lesion resembles the rheumatic pericarditis. It is, as a rule, less extensive than pericarditis and associated with far less serious consequences. It manifests itself in a number of different forms but is generally accompanied by the accumulation of pleural fluid which may be hemorrhagic particularly in young children and is nearly always rich in fibrin. It bears a close resemblance to tuberculous lesions of the pleura but differs from this last infection in that it does not reveal a thickened hyalinized pleura as an end-stage.

There was noted also a definite tendency for the pleurisy to involve the neighboring area of the lungs producing a subpleural pneumonitis.

The authors have also studied the lesions that occur in and about the pulmonary vessels and have found in these patients that there are many arterial changes. They have noted particularly in the cases occurring in childhood the presence of focal or hemorrhagic lobular pneumonia exhibiting certain atypical features. These features differ from ordinary terminal lobular pneumonia. While not specific manifestations of rheumatic fever, these lesions seem to occur fairly commonly in the disease.

Cecil, Russell L., Nicholls, Edith E., and Stainsby, Wendell J.: Bacteriology of the Blood and Joints in Rheumatic Fever. J. Exper. Med. 50: 617, 1929.

During the spring of 1928, 29 patients with acute rheumatic fever were subjected to blood cultures; 9 or 31 per cent yielded a streptococcus. During the spring of 1929, 31 patients with acute rheumatic fever were studied by blood cultures; 26, or 83.9 per cent yielded a streptococcus. The higher percentage of positive cultures in the later series appears to have been due to improved cultural methods. Of the 35 strains of streptococci recovered from blood cultures, 33 have been classified as Streptococcus viridans, one as a Streptococcus hemolyticus and one a Streptococcus anhemolyticus. In 7 patients with rheumatic fever who were subjected to cultures from affected joints, 5 or 71.4 per cent yielded a Streptococcus viridans. In 3 patients in whom green streptococci were recovered from both blood and joint, agglutination and absorption tests proved the identity of the strains isolated from the two sources.

These findings, the authors feel, make it difficult to escape the conclusion that rheumatic fever is a streptococcal infection, usually of the alpha or viridans type and at least in its acute stage is a bacteremia with streptococci circulating in the blood stream.

The authors suppose that in rheumatic fever the patient's tissues are allergic to streptococci while in infectious endocarditis (subacute bacterial endocarditis), the tissues are immune to these organisms. A state of allergy toward the streptococcus, however, will probably not in itself induce the lesions or joint manifestations of rheumatic fever without the concomitant presence of streptococci.

Dressler, Wilhelm, and Fischer, Robert: Tricuspid Stenosis. Klin. Wchnschr. 8: 1267, 1316, 1929.

In a very complete clinical and pathologic study, with an excellent review of the literature, the authors conclude that tricuspid endocarditis, resulting in stenosis, is a much more frequent lesion than the textbooks would have us believe. Among their endocarditis cases, they found tricuspid stenosis (with insufficiency) in 24 per cent. Pure tricuspid insufficiency is rarer than tricuspid stenosis which is usually combined with insufficiency.

Tricuspid stenosis is usually combined with mitral stenosis and very often also with an aortic lesion. The tricuspid lesion never reaches the severe grade of a mitral stenosis, but the right auricle becomes greatly dilated and hypertrophied. The left auricle is usually not so large as it would be in a pure case of mitral stenosis.

The most frequent cause is acute rheumatic fever, and the female sex suffers predominately.

The most important diagnostic signs are: persistent cyanosis, subicteric tint and liver enlargement, which symptoms persist even after edema and other evidences of decompensation disappear. Of great value is a double-phased liver pulsation with an auricular and ventricular component. This sign is regarded as of much greater significance than the venous pulse. A very constant symptom is a considerable enlargement of the heart to the right side with a regular pulse in spite of a severe

associated mitral stenosis. By x-ray the heart is found enlarged to the right; in many cases, there appear no evidence of pulmonary congestion and very little widening of the left auricle.

Tricuspid stenosis definitely adds to the gravity of a pre-existing heart lesion. Nevertheless, compensation may be kept up for years. Thus, Hiller reports a case of a woman fifty-three years old who had 3 attacks of rheumatic fever between nineteen and twenty-nine years. Between twenty-four and thirty-seven, she gave birth to 10 children and continued with her work. After forty-six years of age, she complained of precordial distress but continued to work until eight days before her death.

Adams, Leyland J.: Tuberculosis of the Aorta. Arch. Int. Med. 44: 711, 1929.

The case reported here is one of 33 to be found in the literature where tuberculous lesions have been found in the aorta. The present case is the twentieth instance of tuberculosis reaching the aorta by extension from a tuberculous process outside the aorta.

In this case, the autopsy showed that the involvement extended to the media but that no rupture had occurred. Acute miliary tuberculosis was not present. The lesion had extended from an extensive acute tuberculous involvement of the left pleura.

Clinically, syphilitic aortitis was suspected on account of the history, shortness of breath, pain, pallor and the positive Wassermann reaction.

Anderson, Alan R.: Electrocardiographic Studies in Artificial Pneumothorax and Thoracoplasty. Am. Rev. Tubere. 20: 728, 1929.

Electrocardiograms made on 100 consecutive admissions to a tuberculosis sanitorium have shown very little deviation from the normal. Electrocardiographic studies were made on 50 patients with artificial pneumothorax and 8 cases with thoracoplasty. Neither the degree of pulmonary collapse maintained nor the duration of the collapse therapy had any definite relationship to the form of the electrocardiogram. Axis deviation of the heart occurred with right pneumothorax in 36 per cent of the cases.

These studies would not indicate that any of the patients were afflicted with a degeneration of the cardiac muscle. The clinical data would appear to bear out this contention.

Goldring, William: Edema in Congestive Heart Failure. Effectiveness of Diuretics as a Guide to Prognosis. Arch. Int. Med. 44: 465, 1929.

In a series of 46 patients with congestive heart failure in whom edema was not relieved by digitalis, diuretics were successful in 25 cases (54 per cent). While cardiac edema can generally be relieved by digitalis and rest in bed in most instances, in those patients in whom digitalis is ineffective diuretics may be produced frequently by drugs belonging to the xanthine group. The author believes that of these drugs theophylline and merbaphen in combination with ammonium chloride have been most useful.

Merbaphen is a double salt of sodiumoxymercuriochlorphenoxy acetate with diethyl barbituric acid, containing about 33.9 per cent of mercury in a complex nonionizable combination employed in a 10 per cent solution. It is best used in combination with ammonium chloride. This drug should be used with precaution when there is an associated nephritis, hypertension, exudate or hemorrhage in the retinas and even in the case of elderly persons.

The greatest incidence of reaction was noted in the rheumatic group with persistant cardiac activity. This observation is in contrast to that made by Marvin in a similar group of patients. The author believes that the cessation of diuretic effect from other drugs before edema is completely relieved is due to a temporary depletion of blood chloride. The diuresis following the use of sodium or ammonium chloride in combination with diuretic drugs indicates that the blood chloride level is raised above the renal threshold.

The failure of reaction to adequate digitalization indicates a marked diminution of cardiac reserve. Even when the patients subsequently reacted to a diuretic by complete relief from edema, length of life exceeded six months in only one of the forty-six patients. This observation compares with those made by Marvin in his group of patients.

Burnett, Clough Turrill, and Piltz, George F.: The Electrocardiogram in the Acute Infections. J. A. M. A. **93:** 1120, 1929.

The authors have studied a series of 100 patients who, following some acute infection, were especially studied with reference to possible heart injury. None of these had showed any signs or symptoms of heart disease prior to the recent infection. No cases of scarlet fever, diphtheria or frank rheumatism were included, and none of these patients gave a history of rheumatic fever. Twenty-eight of these furnished significant changes in the electrocardiogram. The changes consisted of prolongation of the P-R interval to or beyond 0.20; inversion of the T-wave in one or more leads; slurring or bizarre R-waves or low voltage in more than one lead, premature beats and sinus block. In 20 of these patients symptoms and other signs of heart disease were lacking or confusing and in only 3 of the 28 were either heart signs or symptoms sufficient to indicate heart injury.

While the occurrence of these changes in the electrocardiogram may or may not indicate pathological changes in the heart, the authors regard them as significant.

They believe that pathological and clinical evidence supports the view that in the course of many types of acute infection, the heart tissues are injured. The electrocardiogram offers a means of diagnosis in a sufficiently large proportion of these cases to render its more general employment worth while.

Book Reviews

Applied Electrocardiography. By Aaron E. Parsonnet and Albert S. Heiman. New York, 1929, The Macmillan Company.

The material of this book is divided into three main sections. The first of 51 pages is devoted to a discussion of the physiological basis of electrocardiography, the electrocardiograph, its description and technic. The latter subject is presented in considerable detail since many of the minor points about conducting a "heart station" are described. While such descriptions may seem superfluous to advanced readers, the points taken up are essential to those beginning the subject and would prove invaluable on such occasions. The second section of 130 pages is devoted to a discussion of the various disorders of the heart, disturbances of the conducting system, diseases of the ventricle and disturbances of coronary circulation. These subjects are presented in the usual manner with electrocardiograms illustrative of each phase of the condition. One hundred and twenty illustrations are included in the text. These reproductions of the electrocardiograms are for the most part clear and ample. A discussion of the various conditions included is brief and met in such a way as to be easily understood by those not necessarily familiar with the "trade terminology" of electrocardiography. There is a short section devoted to a schema for electrocardiographic reading. This book should appeal especially to physicians and students desiring a general information about the subject of electrocardiography without too much detail as to variations and theoretical discussions. It is complete, it is brief, it is ample, and it should be useful. The bibliography concludes the volume.

Cardiac Arrhythmias; Clinical Features and Mechanism of the Irregular Heart. By Irving R. Roth. New York, 1928, Paul B. Hoeber, Inc.

In an introduction by Dr. E. Libman, the statement is made that the impulse to prepare this volume came as the result of an exhibit made by Dr. Roth at the meeting of the American Medical Association in May, 1925. The exhibit was widely admired and its importance for purposes of instruction so much appreciated that Dr. Roth was urged to publish his diagrams in book form. This he has done in this volume with sufficient text to describe the anatomy and physiology of the heart, the mechanism and clinical characteristics of the various types of arrhythmias.

Eighty illustrations and five tables are included in a text of 205 pages. The first section is devoted to the anatomy and physiology of the heartbeat. The normal electrocardiogram and its manner of production by instrumental means are discussed. In a second section of cardiac arrhythmias there is a discussion with electrocardiograms illustrating each type including sinus arrhythmia, auriculoventricular heart-block, extrasystolic arrhythmias, paroxysmal tachycardia, flutter and fibrillation and combined arrhythmias. The text is well prepared, is amply illustrated by electrocardiograms and diagrams to show theoretically the explanation of the disorder. The text is brief, is well written and is easy to read.

CLINICAL ASPECTS OF THE ELECTROCARDIOGRAM; A MANUAL FOR PHYSICIANS AND STUDENTS. By Harold E. B. Pardee. New York, 1928, Ed. 2, Paul B. Hoeber, Inc.

In this volume of 235 pages, the author discusses the normal electrocardiogram and its variations and presents a section on the technic of recording the electrocardiogram and the management of the string galvanometer; then follow in turn the changes due to hypertrophy of the auricles and ventricles to myocardial abnormality and the clinical significance of abnormal waves. A section is devoted to disturbances in rate or rhythm, and under this heading are discussed the various irregularities of the heart. Electrocardiograms illustrative of each disorder are shown by illustration; the nature of the disturbance and its possible explanation are discussed as well as treatment. An important section is devoted to a discussion of the clinical aspects of normal rate and rhythm, especially in regard to diagnosis of these conditions without the aid of instrumental means. This very important chapter should prove valuable to those interested in clinical heart disease. The interpretation and clinical application of the electrocardiogram is presented in detail. There are 60 illustrations showing typical electrocardiograms, figures illustrating explanations of the text and the instruments that are in use in electrocardiography. An extensive bibliography adds greatly to the value of the text.

CLINICAL ELECTROCARDIOGRAMS; THEIR INTERPRETATION AND SIGNIFICANCE. By Frederick A. Willius. Philadelphia, 1929, W. B. Saunders Company.

In this volume of 196 pages there are presented all the various types of electrocardiograms found in disturbances of heart mechanism. The subject matter is divided according to the well-recognized types of disturbances of mechanism, and in each type are discussed the various clinical signs, the types of the electrocardiograms produced by the disorder, the nature of the disorder and such treatment as may be

known for its correction. There is included at the end of each section a full bibliography on the subject. There is no discussion of the instruments of technic or the underlying principles of electrocardiography.

The author has collected a large amount of material and has made excellent selections for illustrations of the type to be presented. A discussion on all points of the clinical disorders is full and very broad in its scope. The possible variations and atypical forms are included in the discussion.

The book should serve as an excellent reference volume for clinicians who may find need for interpretation of an electrocardiogram. In addition, it should interest anyone working in electrocardiography.

These four volumes, together with an additional one *Principles and Practice of Electrocardiography*, by Dr. Carl J. Wiggers (AM. HEART J. **5**: 127, 1929), represent a response on the part of workers in electrocardiography and heart disease to the demand for text discussion of the value of the use of string galvanometers in recording electrocardiograms and their interpretation in patients in the treatment of heart disease. This indicates that the demand for such books is widespread and exacting. They supplement the small volume, *Clinical Electrocardiography*, by Sir Thomas Lewis, (London, 1928, Shaw and Sons, Ltd.,) which has now reached its fourth edition. These six volumes are prepared in about the same style allowing for such normal variations as would be expected from authors of such different experiences. Each volume should find its way to the library of workers particularly interested in electrocardiography, and the casual reader must pick and choose the one which appeals most to him. They are all satisfactory from the standpoint of accuracy, completeness and neatness of preparation.

Each author expresses definitely the feeling that string galvanometers are now well-known instruments of precision and are of value in the study of disturbances in mechanism and possibly other diseases of the heart. This subject no longer holds a position of special technic and has now taken its place among other useful means of accurate diagnosis and treatment. Out of the study devoted to clinical electrocardiography has come a better understanding of clinical disorders of the heart: how they may be recognized under ordinary conditions without instrumental means, how they can be probably placed in the general scheme of heart disease, and how they may be used in the treatment of a patient. Without such volumes as are included in this review, disorders of the heart would probably still hold the mys-

THE HEART IN MODERN PRACTICE, DIAGNOSIS AND TREATMENT. By William Duncan Reid. Philadelphia and London, Ed. 2, 1929, J. B. Lippincott.

This book according to the preface, is an attempt to summarize for the practitioner our knowledge of the diagnosis and treatment of

cardiac diseases, with emphasis upon the contributions to this field which have been made in recent years by the introduction of graphic methods and by intensive studies in other directions.

In spite of a good many defects it fulfils this purpose fairly well. The chief criticisms of the reviewer are that the material is poorly organized, there is much evidence of carelessness in wording which results in vagueness and often in misleading statements, and the treatment is uneven so that some important subjects are inadequately discussed.

By organization of material the reviewer refers to the arrangement of the material in the discussion of individual conditions or syndromes as well as to the arrangement of the book as a whole. The emphasis placed upon etiology is commendable, but it seems that this object could have been attained with less repetition and confusion and with greater evenness of treatment than the author has achieved by the arrangement which he has adopted.

As examples of careless wording the following sentences may be cited: "The direction of the wave, as mentioned above, is also dependent upon which electrode first received the current" (page 47). "Since the chief action of the drug (digitalis) is to produce therapeutic heart-block, its administration will rarely prove of value save in cases of accelerated rate of supraventricular origin" (page 108). "Angina pectoris is a clinical entity that is absent after death" (page 387).

As an example of unevenness in treatment resulting in inadequate discussion of an important subject, the discussion of congestive cardiac failure on page 354 may be cited. It is limited to a single page. At the bottom of the page the statement is made that the treatment and other details of heart failure are sufficiently considered in other parts of the book. The index refers under heart failure to pages 20, 33, 78, 189, and 93 as well as to page 354. Reference to these pages does not help the reader to gain a comprehensive idea of the subject.

From the standpoint of the practitioner heart failure is, however, the most important subject that the author could discuss, and the consideration of it should not be so scattered as to be not easily accessible.

The reviewer also feels that in the section on the cardiac irregularities and in some measure in other sections the author is weak in the discussion of the physiological fundamentals.

—*F. N. W.*